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SENSITIVITY OF RESPIRATORY CENTER TO CARBON DIOXIDE IN EMPHYSEMA AND COR PULMONALE: EFFECTS OF CARBONIC ANHYDRASE INHIBITION

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FOR many years we have been familiar with the fact that patients with chronic cor pulmonale, secondary to pulmonary emphysema, may have a decreased ventilatory response to CO_2 inhalation.[1-5] As early as 1920, Scott[1] pointed out this phenomenon, which he attributed to increased buffering capacity of the blood. It is a well-known fact that these patients may have a normal or low total or alveolar ventilation in the face of an increased arterial P_{CO_2}, as if the usual mechanism for control of arterial P_{CO_2} is disrupted.

Several hypotheses have been presented to explain these facts:

1. Disturbances in the mechanics of breathing, with increased resistance to air flow, may limit ventilation of the patient, as resting ventilation approaches his maximal breathing capacity.
2. Increase in bicarbonates, as renal compensation to respiratory acidosis develops, may diminish the change in hydrogen-ion concentration[1] that normally appears with any CO_2 increase. This would then appear as a decreased response to CO_2. Higher hemoglobin concentration, as in polycythemia, may also act as a buffer.
3. The higher ventilation produced by CO_2 may decrease the anoxia, and so suppress the anoxic potentiation of the respiratory center, thus conterbalancing the direct action of CO_2 upon the center.[4,5]
4. The respiratory center may become acclimated to a chronically elevated P_{CO_2}, so that its capability of perceiving a change in arterial PCO_2 will be blunted.[6-8]
5. The relationship $BHCO_3/CO_2$ seems to be all important in respiratory center stimulation by CO_2.[9] Increase in bicarbonates might be able to decrease the excitation produced by CO_2.

The present article is based on the study of pulmonary ventilation and blood gases in normal subjects and in cases of chronic cor pulmonale secondary to pulmonary emphysema in acute or chronic respiratory acidosis. The sensitivity of the respiratory center to CO_2 is evaluated by the change in ventilation

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induced by breathing CO_2 in air which brings about an acute increase in arterial P_{CO_2}. An analysis is made of the factors responsible for this response and the modifications which can be exerted on it by pharmacologic depletion of blood bicarbonates by means of acetazoleamide.

METHODS

Repeated observations were made on 4 normal adults, one emphysema patient in acute respiratory acidosis with cor pulmonale in heart failure, and 6 other emphysema patients—4 of them in Baldwin[10] and colleagues' Group 4, one in Group 1, and one in Group 3. In all the cases with pulmonary disorders, vital capacity and maximal breathing capacity were reduced, in agreement with generally reported data. All the determinations were made with patients in basal conditions, recumbent, and thoroughly familiarized with the proceedings to be carried out. Respiratory variables were measured by collection of expired air in a Tissot gasometer or Douglas bag, by means of a mouthpiece and low-resistance, two-way respiratory valve. Arterial blood was collected through an indwelling needle placed in a femoral or brachial artery during the 3-minute period of gas collection. Effective alveolar ventilation was computed by application of Bohr's equation for physiologic dead space, assuming equality between arterial and alveolar P_{CO_2}.[11] Oxygen consumption, CO_2 output, and respiratory exchange ratio were determined at the same time through analysis of expired gas by the Haldane or Scholander techniques. Arterial O_2 and CO_2 content was measured by means of the Van Slyke manometric apparatus. Oxygen capacity was determined by exposing arterial blood to a P_{O_2} of 190 mm. Hg in a closed tonometer at 37° C. Carbon dioxide combining power was determined by exposing whole blood to a P_{CO_2} of 40 mm. Hg in the same tonometer where the O_2 capacity was measured. Henderson's nomogram was used for determination of the P_{CO_2} of arterial blood, knowing the CO_2 and O_2 content, and the tension in the equilibrated blood.[12,13] Carbon dioxide content of plasma was calculated from the values of the CO_2 content of the blood at 40 mm. Hg and O_2 capacity, using the chart of Henderson; pH was computed by Henderson-Hasselbach equation.

After collection of blood and expired gas, the patient inhaled a mixture of approximately 5 per cent CO_2 in air during a period of 20 to 30 minutes, and the same procedure carried out previously was repeated. The CO_2 mixture was supplied from a Tissot gasometer with a capacity of 500 liters.

In some patients, inhalation of "pure" O_2 and 5 per cent CO_2 in oxygen was also carried out, and arterial blood and expired gas were collected after 30 minutes.

Symbols used in the tables and figures are those recommended by a meeting of American physiologists.[14]

Acetazoleamide was administered in a dosage of 12 to 15 mg. per kilogram per day in 3 or 4 divided doses for 2 to 15 days. The procedures outlined were then repeated.

RESULTS

Results obtained in normal persons may be seen in Tables I and II in which ventilatory data and blood gas values are given.

In Fig. 1 may be observed the ventilatory ratio $\left(VR = \frac{V_{E CO_2}}{V_E air}\right)$ opposed to inspired CO_2 partial pressure; heavy lines limit the expected values for ventilatory response. A patient with metabolic acidosis who did not tolerate 5 per cent CO_2 was studied on 3 per cent CO_2 and had a higher ventilation than expected.

Ventilatory response to CO_2 inhalation was normal in the 2 young subjects, and somewhat less than normal in E.V. and M.C.C. (Mean change was 2.7 times increase in resting total ventilation and 2.9 times for alveolar ventilation.

Tables V and VI, Fig. 2). The volume of physiologic dead space was increased by CO_2 by about 70 per cent above the control values (Table VI). In all cases there was a small decrease in oxygen uptake during CO_2 breathing. The respiratory exchange ratio decreased with CO_2 in all instances, probably showing that a steady state had not been attained completely and that some of the inspired CO_2 was retained in the body. The oxygen saturation of arterial blood increased slightly in all cases, arterial P_{CO_2} increase was about 6 mm. Hg in the two young subjects and about 10 mm. Hg in the other two (Tables V and VI). Blood bicarbonate increase was not completely compensatory, so that pH values showed decreases between 0.04 and 0.1 in pH units.

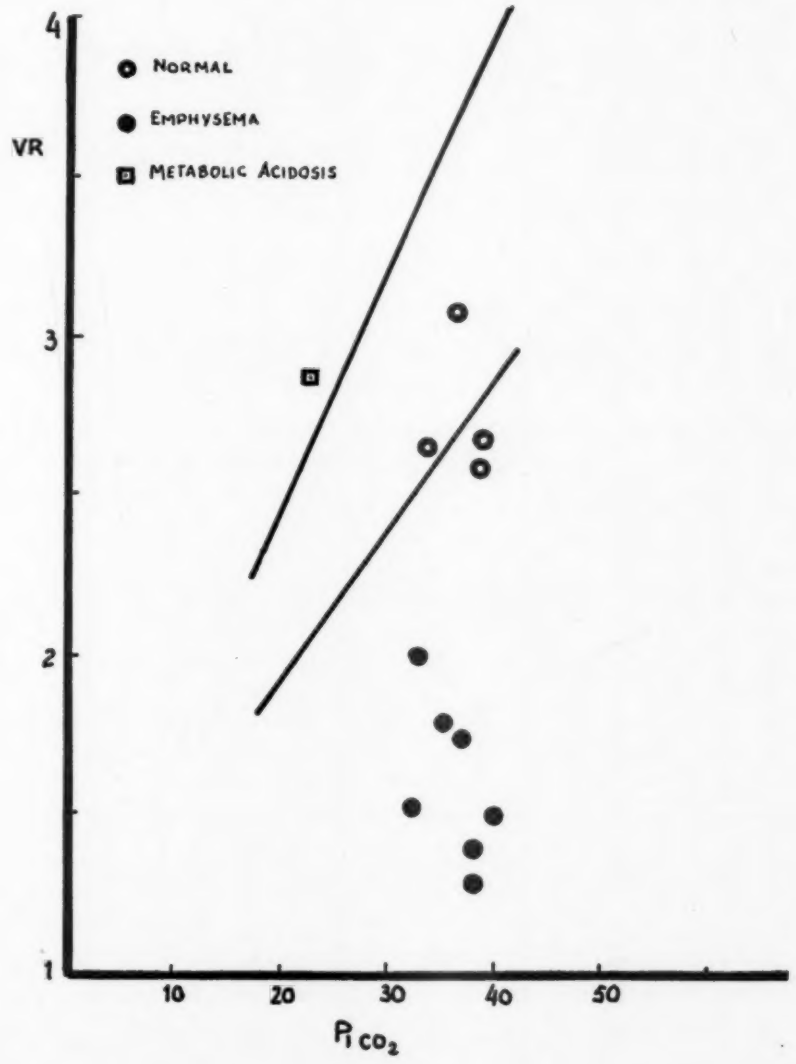

Fig. 1.—Ventilatory response to CO_2 inhalation is demonstrated by the relationship between pressure of CO_2 in inspired gas and change in total ventilation provoked (1 in ordinate represents basal ventilation). Heavy lines limit the normal response.

TABLE I. RESPIRATORY DETERMINATIONS IN NORMAL SUBJECTS BEFORE AND AFTER 6063 ADMINISTRATION

SUBJECTS	SEX	AGE	B.S.A.	DETERMINATION		$\dot{V}_E$/M.²†	$\dot{V}_A$/M.²†	V_D (ML.)	$\dot{V}_{O_2}$/M.² (ML.)	$\dot{V}_{CO_2}$/M.² (ML.)	R.Q.	$\Delta\dot{V}E$ / ΔPa_{CO_2}	$\Delta\dot{V}A$ / ΔPa_{CO_2}	$\Delta\dot{V}A$ / $\Delta[H]^+$
E.V.	M.	52	1.51	Control	Air	4.60	2.60	179	163	115	0.71	0.61	0.47	0.53
					CO_2 5.5%	11.1	7.57	301	155	89	0.58			
				Fourth* Day	Air	5.12	2.89	172	148	98	0.66	0.68	—	—
					CO_2 6.3%	18.2	—	—	—	—	—			
M.B.	F.	20	1.45	Control	Air	4.21	2.85	116	153	117	0.77	1.5	—	—
					CO_2 5%	13.25	—	—	140	105	0.75			
				Fourth* Day	Air	5.08	4.44	81.8	142	117	0.83	0.89	—	—
					CO_2 5%	20.60	—	274	—	84	—			
M.C.C.	F.	48	1.52	Control	Air	4.80	2.69	213	145	116	0.80	0.64	0.50	0.61
					CO_2 5.6%	12.50	7.87	391	132	—	—			
				Second* Day	Air	4.90	3.01	201	118	106	0.90	0.73	0.57	1.07
					CO_2 5%	13.86	9.95	283	136	86	0.64			
D.B.	F.	25	1.64	Control	Air	3.64	2.87	126	142	116	0.81	0.94	—	—
					CO_2 4.6%	9.76	—	—	132	105	0.80			
				Seventh* Day	Air	3.76	2.56	176	126	95	0.76	1.33	1.24	1.45
					CO_2 4.6%	14.85	12.59	201	156	112	0.71			

*Days of 6063 administration.
†Liters per minute.

TABLE II. ARTERIAL BLOOD DETERMINATIONS IN NORMAL SUBJECTS BEFORE AND AFTER 6063 ADMINISTRATION

SUBJECT	DETERMINATION	INHALING	Hb O_2 CAPACITY	Sa_{O_2}	Pa_{CO_2}	$BHCO_3$	H_2CO_3	pH	$[H]^+$
E.V.	Control	Room air	18.19	92.9	38.5	57.14	2.66	7.44	36.31
		CO_2 5.5%	18.19	94.0	49.0	60.25	3.64	7.34	45.71
	Fourth Day*	Room air	18.22	94.7	31.8	39.37	2.21	7.35	44.67
		CO_2 6.3%	19.03	93.5	51.0	44.99	3.54	7.21	54.96
M.B.	Control	Room air	16.54	94.6	35.5	50.25	2.47	7.40	39.82
		CO_2 5%	16.78	99.1	41.5	51.69	2.89	7.36	44.95
	Fourth Day*	Room air	15.55	95.5	24.5	35.42	1.71	7.41	38.91
		CO_2 5%	15.66	94.9	42.0	39.67	2.92	7.26	54.96
M.C.C.	Control	Room air	17.01	94.0	37.5	52.11	2.61	7.40	39.82
		CO_2 5.6%	16.78	97.4	47.0	56.05	3.27	7.34	45.71
	Second Day*	Room air	16.46	93.3	30.4	40.02	2.11	7.38	41.69
		CO_2 5%	16.49	95.8	43.0	43.55	2.99	7.27	53.71
D.B.	Control	Room air	20.57	95.0	35.0	49.80	2.33	7.43	37.16
		CO_2 4.6%	20.18	96.8	41.5	52.16	2.89	7.39	40.74
	Seventh Day*	Room air	20.51	93.1	31.7	36.30	2.20	7.32	47.87
		CO_2 4.6%	20.95	95.8	40.0	39.70	2.78	7.26	54.96

*Days of 6063 administration.

TABLE III. RESPIRATORY DETERMINATIONS IN PATIENTS WITH COR PULMONALE BEFORE AND AFTER 6063 ADMINISTRATION

PATIENT	SEX	AGE	B.S.A.	DETERMINATION		$\dot{V}_E$/M.²†	$\dot{V}_A$/M.²†	V_D (ML.)	$\dot{V}_{O_2}$/M.² (ML.)	$\dot{V}_{CO_2}$/M.² (ML.)	R.Q.	$\Delta\dot{V}_E$ / ΔPa_{CO_2}	$\Delta\dot{V}_A$ / ΔPa_{CO_2}	$\Delta\dot{V}_A$ / $\Delta[H]^+$
A.M.P.	F.	68	1.43	Control	Air	4.22	1.29	161	127	108	0.85	0.13	0.026	0.032
					CO_2 5.6%	6.50	1.72	236	118	85	0.72			
				Fourteenth* Day	Air	4.50	1.83	119	147	115	0.78	0.12	0.057	0.065
					CO_2 5%	6.20	2.59	198	124	89	0.71			
E.D.	M.	30	1.57	Control	Air	3.80	1.93	138	190	150	0.79	0.64	0.49	0.61
					CO_2 5%	6.70	4.18	184	241	175	0.73			
				Seventh* Day	Air	4.25	2.11	182	192	150	0.78	0.73	0.57	1.07
					CO_2 4.8%	7.55	4.66	193	190	170	0.89			
J.S.	M.	52	1.83	Control	Air	3.52	1.41	202	142	114	0.81	0.23	0.145	0.16
					CO_2 4.5%	5.71	2.79	254	117	111	0.94			
				Seventh* Day	Air	3.85	1.71	209	132	101	0.76	0.42	0.17	0.27
					CO_2 4.9%	7.47	3.24	370	100	93	0.93			

A.S.	M.	40	2.25	Control	Air	4.80	—	—	181	—	0.74	—	—	—
					CO_2 5%	6.50	—	—	—	—	—	—	—	—
				Ninth* Day	Air	4.43	—	—	151	—	0.77	—	—	—
					CO_2 5%	9.35	—	—	—	—	—	—	—	—
L.G.R.	F.	48	1.51	Control	Air	6.4	1.80	175	187	134	0.71	—	—	—
					CO_2 5%	8.6	—	—	—	—	—	—	—	—
				Seventh* Day	Air	4.9	1.69	155	138	106	0.77	—	—	—
					CO_2 5%	8.5	—	—	—	—	—	—	—	—
J.M.	M.	52	1.71	Control	Air	4.11	2.03	209	139	118	0.85	0.21	0.097	0.14
					CO_2 5%	7.30	3.47	397	135	106	0.78			
				Ninth* Day	Air	4.30	2.29	223	127	108	0.86	0.57	0.300	0.63
					CO_2 5%	10.00	5.56	446	137	106	0.75			

*Days of 6063 administration.
†Liters per minute.

TABLE IV. ARTERIAL BLOOD DETERMINATIONS IN PATIENTS WITH COR PULMONALE BEFORE AND AFTER 6063 ADMINISTRATION

PATIENT	DETERMINATION	INHALING	Hb O_2 CAPACITY	Sa_{O_2}	Pa_{CO_2}	$BHCO_3$	H_2CO_3	pH	$[H]^+$
A.M.P.	Control	Room air	19.49	69.6	66.0	83.88	4.60	7.37	42.66
		CO_2 5.6%	20.16	84.9	82.5	80.94	5.76	7.25	56.24
	Fourteenth Day*	Room air	17.17	78.4	54.5	66.70	3.80	7.35	44.67
		CO_2 5%	17.50	85.9	68.5	67.09	4.75	7.25	56.24
E.D.	Control	Room air	29.24	65.4	68.0	71.76	4.73	7.29	51.29
		CO_2 5%	29.59	83.1	72.5	71.56	5.04	7.26	54.96
	Seventh Day*	Room air	30.02	77.6	61.5	58.33	4.28	7.23	58.89
		CO_2 4.8%	30.09	88.0	66.0	59.51	4.60	7.22	60.26
J.S.	Control	Room air	21.54	71.3	57.0	71.80	3.97	7.37	42.66
		CO_2 4.5%	21.66	87.9	66.5	71.94	4.63	7.30	51.29
	Seventh Day*	Room air	21.35	83.9	51.0	48.25	3.61	7.23	58.89
		CO_2 4.9%	21.31	92.6	60.0	50.73	4.18	7.19	64.57
A.S.	Control	Room air	22.40	37.8	97.5	78.00	8.20	7.18	66.07
		CO_2 5%	—	—	—	—	—	—	—
	Ninth Day*	Room air	21.92	87.0	50.5	62.27	3.51	7.35	44.67
		CO_2 5%	—	—	—	—	—	—	—
L.G.R.	Control	Room air	24.4	40.6	62.5	82.0	4.35	7.38	41.70
		CO_2 5%	—	—	—	—	—	—	—
	Seventh Day*	Room air	24.53	73.6	59.0	70.29	4.10	7.34	45.72
		CO_2 5%	—	—	—	—	—	—	—
J.M.	Control	Room air	21.05	85.4	47.5	66.48	3.30	7.40	39.82
		CO_2 5%	20.55	94.8	62.3	66.87	4.33	7.30	50.12
	Ninth Day*	Room air	20.50	90.5	41.1	45.76	2.86	7.31	48.98
		CO_2 5%	20.29	91.7	52.0	47.53	3.62	7.23	58.89

*Days of 6063 administration.

The relationship between ventilation and arterial P_{CO_2} was demonstrated by the change in total ventilation ($\dot{V}_E/M.^2$) associated with 1 mm. Hg rise in arterial P_{CO_2}. This index showed normal values of around 1.22 L./M.^{2} in the two young subjects and lower figures (0.62 L./M.^{2}) in the two older ones (Tables I and VI).

Results obtained in the second group of patients with emphysema are shown in Tables III and IV. While total ventilation was normal or higher, control alveolar ventilation was lower than normal in patients A.M.P. and J.S. On the other hand, on CO_2 inhalation the total ventilation mean increase was only 54 per cent, much lower than that observed in normals. Alveolar ventilation increase was 82 per cent (Tables V and VI).

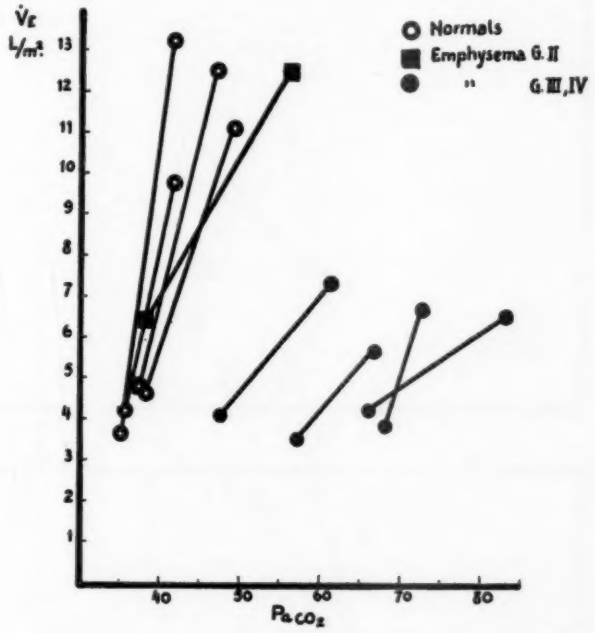

Fig. 2.—Change in $\dot{V}_E$ vs. Pa_{CO_2} after 5 per cent CO_2 inhalation. Change in total ventilation as a function of the increase in arterial P_{CO_2} with CO_2 inhalation.

The volume of "physiologic" dead space suffered a mean increase of 49 per cent over control figures, on breathing CO_2 (Table VI). Oxygen uptake did not show any constant trend, while the respiratory exchange ratio tended to decrease in all cases except one (J.S.). The arterial oxygen saturation which had a mean initial value of 73 per cent (excluding two cases with acidosis) (Table V) increased markedly in all patients, without reaching normal values, however, except in one patient (J.M.). Arterial P_{CO_2} (mean initial value 58.1 mm. Hg excluding one case with 97.5 mm. Hg) also increased more than in normal subjects, producing a further lowering of pH. The change in total ventilation per millimeters of mercury of P_{CO_2} increase $\left(\frac{\Delta \dot{V}_E}{\Delta Pa_{CO_2}}\right)$ had a mean value of only 300 c.c. (Table VI), including patient E.D. where a bigger than expected change

was observed (see discussion). This index amounted to 189 c.c. for alveolar ventilation. In Fig. 3 ventilation $\left(as\ V_E R\cdot \frac{\dot{V}_{ECO_2}}{\dot{V}_E\ air}\right)$ is opposed to arterial P_{CO_2} (lower abscissas) and $C[H]^+$ (upper abscissas). Changes in ventilation and arterial P_{CO_2} during CO_2 inhalation are compared with changes in $C[H]^+$ and it can be seen that the hydrogen-ion concentration increases markedly so

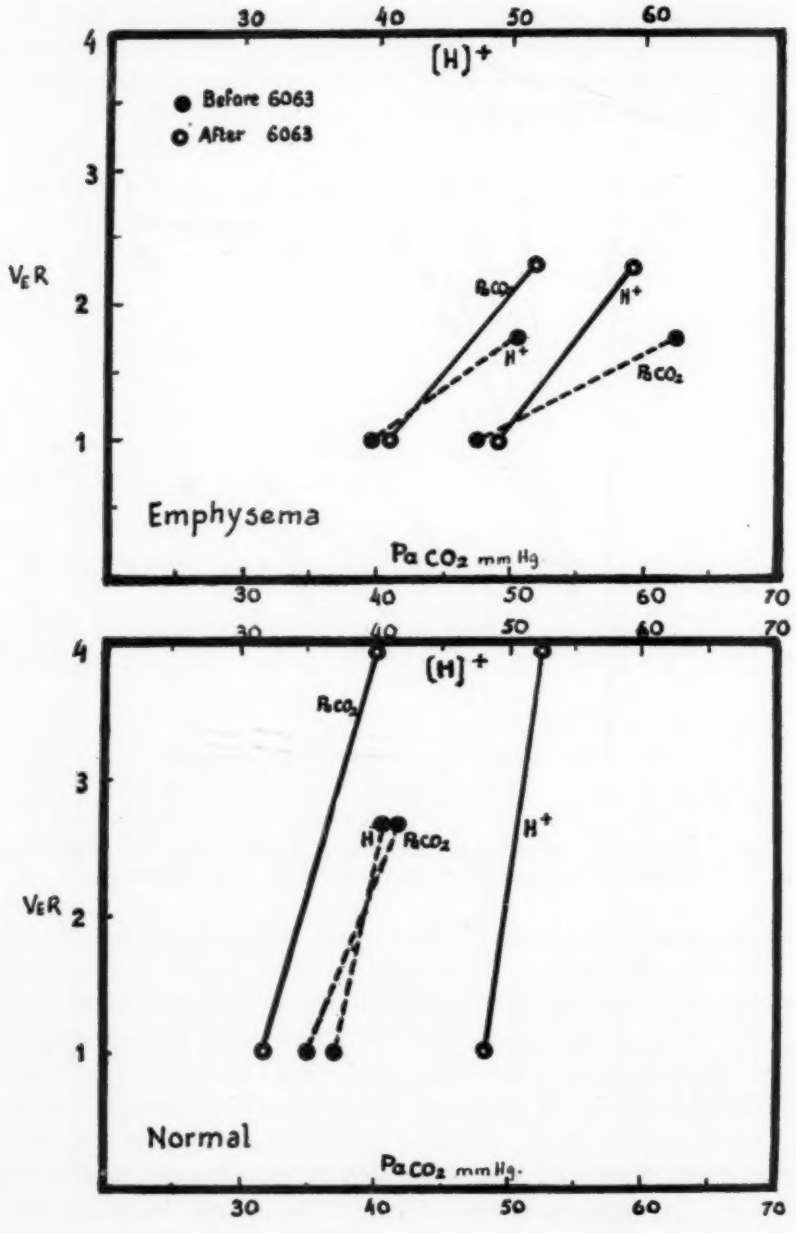

Fig. 3.—Change in $\dot{V}_E$ as a function of change in Pa_{CO_2} or $[H]^+$ during CO_2 inhalation. Ventilatory response to CO_2 inhalation expressed as a function of the change in P_{CO_2} or $[H]^+$ in arterial blood. A normal subject is shown in the lower part, an emphysema case in the upper part of the figure.

that ventilation is depressed in terms of this variable as well as of arterial P_{CO_2}. There is an inverse relationship between resting arterial P_{CO_2} level and the sensitivity index (Fig. 4) expressed in terms of change in total ventilation, alveolar ventilation, or hydrogen-ion concentration.

Some of the cases with acute or chronic acidosis (Pa_{CO_2} higher than 50 mm. Hg) were submitted to inhalation of different gas mixtures in order to measure ventilatory response and allied changes in blood gases from a therapeutic angle. The mixtures used were: "pure" O_2, 5 per cent CO_2 in air,

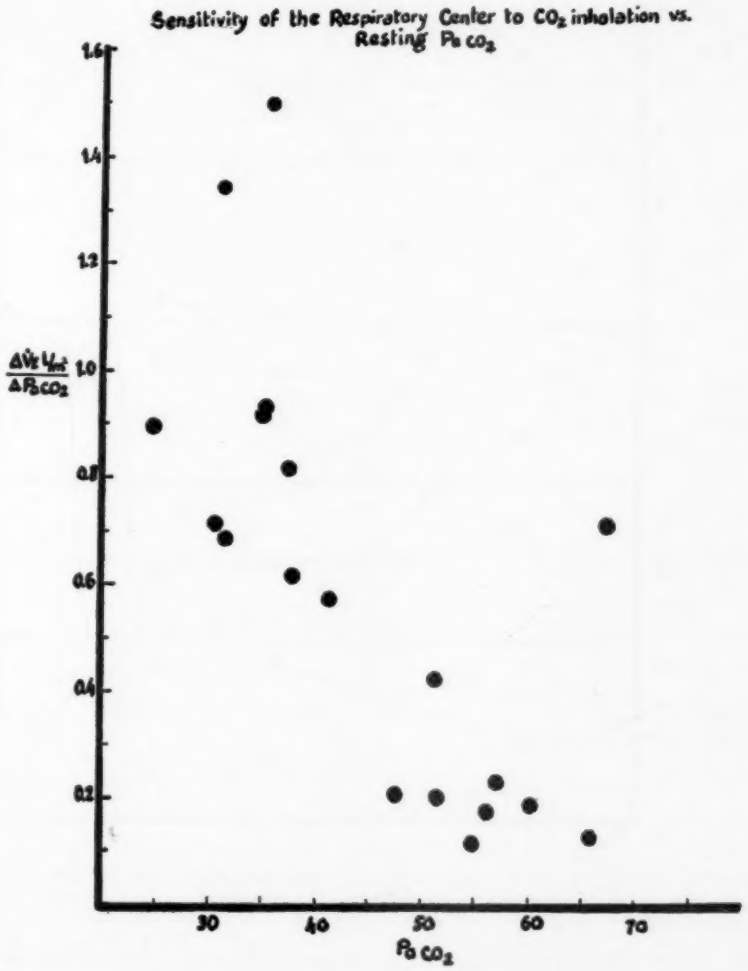

Fig. 4.—Relationship between the sensitivity of the respiratory center represented by a ventilatory index (see text) and the basal arterial P_{CO_2} of the subjects.

and 5 per cent CO_2 in oxygen. Changes observed in respiratory variables and blood gases are presented in Table VII. Ventilatory and blood gases modifications for one representative case are illustrated in Fig. 5. A very characteristic pattern can be summarized: total and alveolar ventilations fall on "pure" O_2, with concomitant acute rise in arterial O_2 and fall of pH. On the other hand,

ventilation is always increased by CO_2 in air with some increase in arterial oxygen saturation, Pa_{CO_2} and fall of pH. Carbon dioxide in oxygen elicits intermediate effects with a ventilation that remains near to control value, complete saturation of hemoglobin and high Pa_{CO_2}.

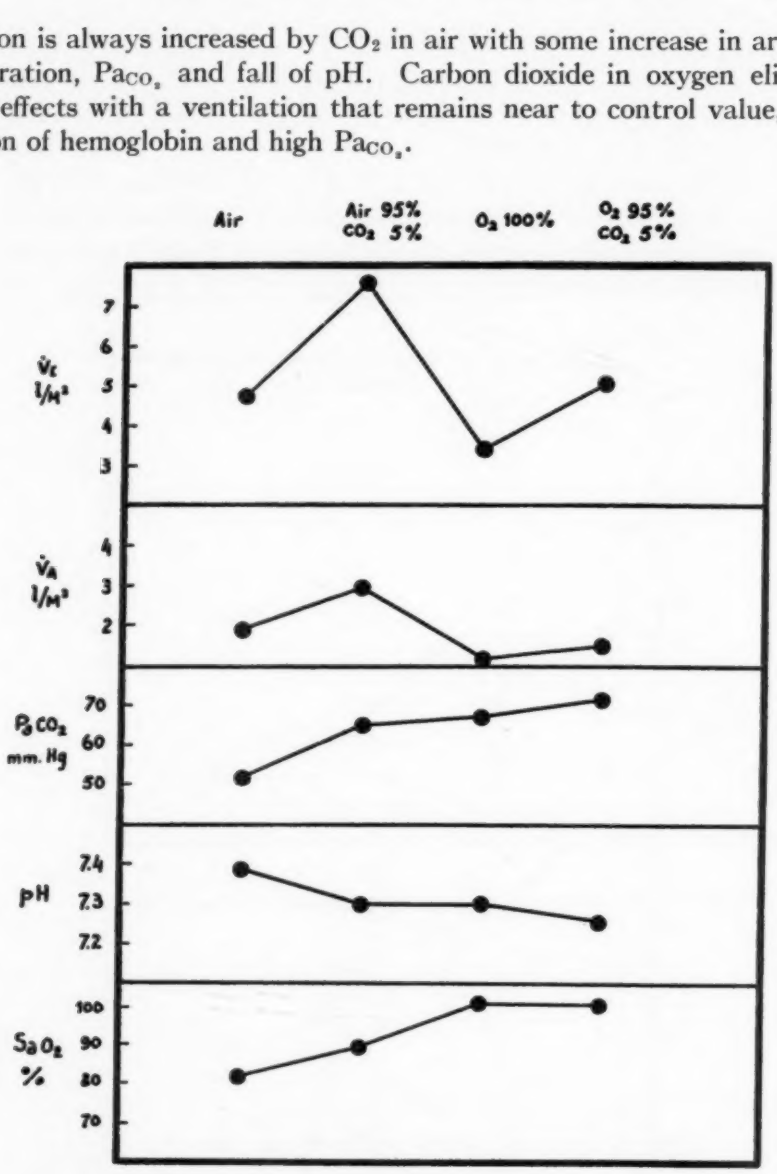

Fig. 5.—Changes in ventilation and blood gases in an emphysema case with chronic respiratory acidosis exposed to different gas mixtures.

Studies were repeated after acetazoleamide was given for several days. Results for normal subjects are shown in Tables I, II, and V. Some increase in total and alveolar ventilation was found in all cases except one (D.B., $\dot{V}_A/M.^2$) reaching 17 per cent as an average for effective alveolar ventilation (Table VI). The volume of "physiologic" dead space tended to decrease in three cases, an inverse change was apparent in D.B.; mean values for the two groups did not show any change (Table VI). Oxygen consumption was lower in all cases, average 11 per cent; and CO_2 elimination decreased 10 per cent on an average; respiratory exchange ratio showed little change. The average arterial P_{CO_2}

fall is 7 mm. Hg and blood bicarbonates decreased 14.5 vol. per cent on the average (Table II, Fig. 6). As the blood bicarbonate decreased proportionately more than the P_{CO_2} fell, pH was lowered by an average of 0.5 pH units (Table V). In these conditions CO_2 inhalation was repeated as an attempt to correlate ventilatory changes with modifications in arterial P_{CO_2} (Fig. 7). Ventilation then increased 3.8 times over resting values (Table V). The index previously described $\left(\frac{\Delta \dot{V}_E \, L./M.^2}{\Delta Pa_{CO_2}}\right)$ showed some increase over the control figures obtained before use of acetazoleamide. However, this change was pronounced in only one case (D.B.); in two others it was small, and in another it was absent (M.B.).

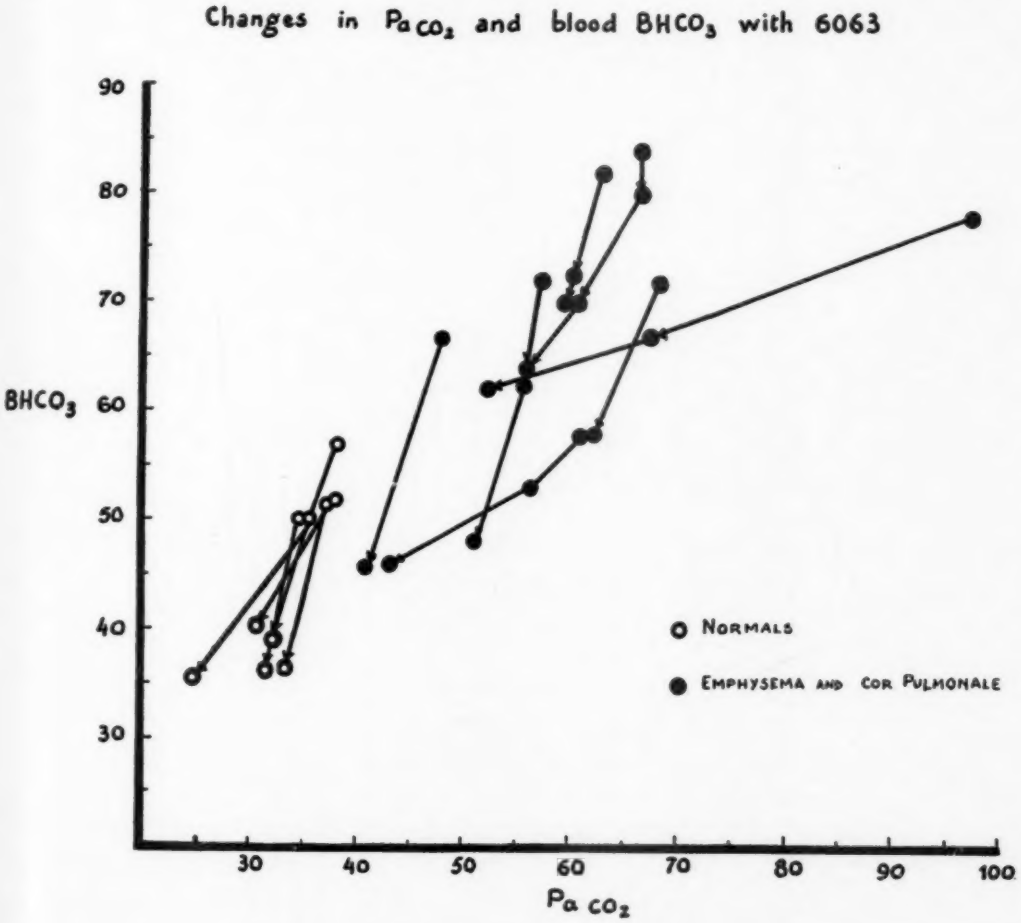

Fig. 6.—Modifications in arterial bicarbonates and P_{CO_2} after the ingestion of acetazoleamide.

It can be seen (Table II) that normal subjects on Diamox show a total ventilation higher or similar to that present in the control state in face of a much lower Pa_{CO_2} (Fig. 7). This situation was repeated with CO_2 inhalation, in which case a same mean arterial P_{CO_2} (Table VI) correlated with a much higher ventilation when the patient had been given 6063 (Fig. 7).

TABLE V. AVERAGE RESPONSE OF NORMAL SUBJECTS AND EMPHYSEMA PATIENTS TO CO_2 INHALATION

INSPIRED GAS		pH		$Paco_2$ INCREASE		Sao_2 VALUES		$\dot{V}_E$ INCREASE (% OF CONTROL)	
		NORMAL	EMPHYSEMA	NORMAL	EMPHYSEMA	NORMAL	EMPHYSEMA	NORMAL	EMPHYSEMA
Control	Room Air	7.41	7.33	—	—	94.1	73.0*	—	—
	CO_2 in Air	7.36	7.28	8.5†	11.3	96.8	87.7	270	154
On 6063	Room Air	7.36	7.30	—	—	94.1	82.6*	—	—
	CO_2 in Air	7.25	7.22	14.4‡	9.9	95.0	89.5	378	186

*Excluding cases of acute acidosis.
†Mean increase in the two young subjects 6.3 mm. Hg.
Mean increase in the two older subjects 10.7 mm. Hg.
‡Considerations about influences upon this value are made under results.

TABLE VI. MEAN VALUES

	NORMALS				EMPHYSEMA			
	AIR		CO_2		AIR		CO_2	
	CONTROL	ON 6063	CONTROL	ON 6063	CONTROL	ON 6063	CONTROL	ON 6063
$\dot{V}_E/M.^2$	4.31	4.46	11.65	16.87	4.47	4.37	6.88	8.17
$\dot{V}_A/M.^2$	2.75	3.22	7.72	11.27	1.66	1.92	3.04	4.01
V_D	158	157.7	346	251	177	177.6	267	301.7
$\dot{V}_{O_2}/M.^2$	150	133.5	139.7	146	161	147.8	152.7	137.7
$\dot{V}_{CO_2}/M.^2$	116	104	99.6	94	124.8	116	119.2	114.5
Pa_{CO_2}	36.6	29.6	44.7	44	66.4*	52.9	70.9*	61.6
$BHCO_3$	52.32	37.77	55.03	41.97	75.65	58.6	72.82	56.21
$\Delta\dot{V}_E/M.^2$ / $\Delta PaCO_2$	0.91	0.90	—	—	0.30	0.46	—	—
RQ	0.77	0.78	0.71	0.67	0.79	0.78	0.79	0.82

*Difference between values for these variables differs from those of Table V, because here all cases were considered and there only those completely studied.

TABLE VII. RESPONSE TO INHALATION OF "PURE" O_2, 5 PER CENT CO_2 IN AIR AND 5 PER CENT CO_2 IN O_2

SUBJECT	BREATHING	DATE	$\dot{V}_E$	$\dot{V}_A$	f	V_D	SaO_2	Pa_{CO_2}	$BHCO_3$	pH
A.S.	Room air	April 6, 1955	4.80	—	36	—	37.8	97.2	78.0	7.18
	5% CO_2		6.50	—	—	—	—	—	—	—
	100% O_2		2.24	—	—	—	—	—	—	—
	5% CO_2 in O_2		4.80	—	—	—	—	—	—	—
E.D.	Room air	June 22, 1955	3.80	1.93	22	138.3	65.4	68.0	71.7	7.29
	5% CO_2		6.70	4.17	28	184.2	83.0	72.5	71.5	7.26
	100% O_2		2.80	1.12	15	173.5	$100^{+.17}$	80.0	71.6	7.21
J.S.	Room air	July 13, 1955	3.50	1.41	19	202.3	71.0	57.0	71.8	7.37
	4.5% CO_2		5.70	2.79	21	253.8	87.9	66.5	71.9	7.30
	100% O_2		2.70	1.16	17	167.0	$100^{+.58}$	68.0	70.9	7.28
G.Q.*	Room air	July 22, 1955	4.77	1.93	19	235.5	81.7	51.6	69.8	7.39
	4.7% CO_2		7.51	2.94	22	352.2	89.4	65.0	70.2	7.30
	100% O_2		3.46	1.13	21	173.7	$100^{+.58}$	65.5	70.9	7.30
	4.8% CO_2 in O_2		5.00	1.48	20	275.3	$100^{+.90}$	71.0	71.3	7.26
J.D.*	Room air	Aug. 15, 1955	4.03	—	24	—	70.0	53.2	72.4	7.41
	4.5% CO_2		5.50	—	26	—	—	—	—	—
	100% O_2		3.06	—	22	—	$100^{+.34}$	70.1	74.0	7.30
	CO_2 4% in O_2		4.30	—	22	—	—	—	—	—

*Chronic pulmonary emphysema with compensated cor pulmonale.

$\dot{V}_E$ and $\dot{V}_A$ are expressed in L./M.²/min. V_D in ml. $BHCO_3$ in vol. per cent.

The results obtained with acetazoleamide in patients with cor pulmonale are shown in Tables III and IV. Total ventilation did not change, alveolar ventilation showed a mean increase of 15.7 per cent over control. Oxygen consumption or respiratory exchange ratio did not show a consistent change and CO_2 output decreased (Table VI), though its mean fall was not statistically significant. Arterial P_{CO_2} decreased an average of 6.8 mm. Hg (Table VI), excluding one case of acute acidosis (A.S.) in which the Pa_{CO_2} was lowered by 47 mm. Hg

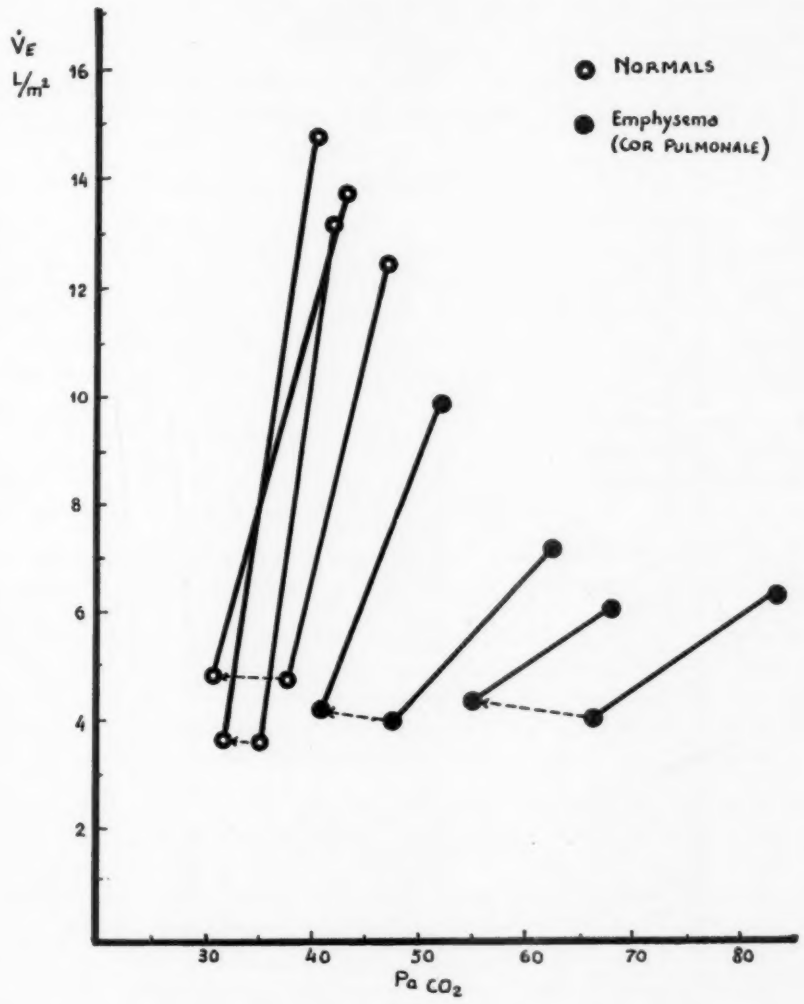

Fig. 7.—Change in $\dot{V}_E$ vs. Pa_{CO_2} during 5 per cent CO_2 inhalation before and after 6063. Ventilatory responses, related to arterial P_{CO_2}, obtained with CO_2 inhalation before and after 6063 in two cases from each group of subjects.

There was a 9.7 per cent increase in saturation (Table V), (the two cases of acute anoxia, A.S. and A.G.R., are excluded). Blood bicarbonates fell a mean of 17 vol. per cent (Fig. 6) and the average lowering of pH was 0.07 pH units (A.S. excluded).

TABLE VIII. EFFECTS OF OXYGEN INHALATION DURING CONTROL AND "6063" PERIODS IN PATIENTS WITH CHRONIC PULMONARY EMPHYSEMA

PATIENT	A. S.				E. D.				J. S.			
PERIOD	CONTROL		"6063"		CONTROL		"6063"		CONTROL		"6063"	
BREATHING	ROOM AIR	100% O_2	ROOM AIR	100% O_2	ROOM AIR	100% O_2	ROOM AIR	100% O_2	ROOM AIR	100% O_2	ROOM AIR	100% O_2
$\dot{V}_E/M.^2$	4.8	−53	5.9	−19	3.8	−26	4.25	−19	3.52	−23	3.85	−2
$\dot{V}_A/M.^2$	—	—	—	—	1.93	−42	2.10	−35	1.41	−17.7	1.70	−11.8
f	36	—	24	—	22	15	18	20	19	17	18	18
SaO_2	37.8	—	75	—	65.4	$100^{+.17}$	77.6	$100^{+.49}$	71	$100^{+.58}$	84	$100^{+1.4}$
$Paco_2$	97.2	—	67.5	—	68	80	61.5	71	57	68	51	58.5
$BHCO_3$ (vol. %)	78	—	67	—	71.7	71.6	58.3	59	71.8	70.9	48.2	49.4
pH	7.18	—	7.26	—	7.29	7.21	7.23	7.18	7.37	7.28	7.23	7.19

$\dot{V}_E$ and $\dot{V}_A$ during "pure" O_2 inhalation are expressed as per cent of control values with room air. O_2 was inhaled during 30 minutes and blood was collected during the last 3 minutes.

f signifies rate of breathing.

Ventilatory response to CO_2 after treatment with 6063 presented some differences. The mean total increase in ventilation (Table V) was 1.8 times and in mean alveolar ventilation 2.08 times over that observed while breathing room air. The volume of "physiologic" dead space increased by 87 per cent (Table VI). Oxygen consumption and CO_2 output fell similarly as in breathing air. Arterial CO_2 tension increased 11.3 mm. Hg as a mean average (Table V). After 6063 the ventilatory response to CO_2, correlated with concomitant changes in Pa_{CO_2} by the index described, showed a slight increase (Table III).

Some patients were restudied breathing "pure" O_2 to evaluate any possible change in their ventilatory response after the decrease in bicarbonates and arterial P_{CO_2} provoked by 6063. The results are presented in Table VIII. It was apparent that ventilation was less depressed after 6063 was administered.

DISCUSSION

The results obtained in normal subjects with CO_2 inhalation are similar to those presented previously.[5] In emphysema patients (with CO_2 retention), the response to CO_2 was much lower than normal in a range similar to that previously found.[1-6,15,16] The observed increase in arterial O_2 saturation in spite of a higher alveolar CO_2 pressure may be dependent on the increase in alveolar ventilation and perhaps better distribution of inspired gas. In all cases the ventilatory response to CO_2 as expressed by the relation between total alveolar ventilation and Pa_{CO_2} change was lower than normal and in a range similar to that observed by others.[15]

The hypotheses proposed to explain this abnormal ventilatory response were presented previously. Emphysema with respiratory insufficiency for CO_2 elimination is marked by a normal or low alveolar ventilation in face of a high Pa_{CO_2}. Sensitivity of the respiratory center to its physiologic stimulator seems depressed.

1. Mechanical impairment does not constitute a possible factor in many cases; our patients had an M.B.C. of 4 to 6 times their resting ventilation while change in ventilation on CO_2 never duplicated the initial value.

2. We have already shown that there is not sufficient buffering power in these patients to nullify the increase in hydrogen-ion concentration (Fig. 3) produced by CO_2 inhalation. Therefore, Scott's hypothesis is not confirmed because there is also a hyposensitivity to hydrogen-ion.[6]

3. The mild relief in anoxemia produced by CO_2 inhalation is not capable of depressing the ventilatory response through decrease in hypoxic stimulation, as has been proved recently by Fishman.[16]

4. Anoxemia might be a motive, but anoxemia is also present in some cases of congenital heart disease and ventilation remains high, resulting in a low arterial P_{CO_2}. Moreover, these patients have a normal response to CO_2 inhalation.[15]

5. Acclimatization to CO_2 in itself or depression produced by increase in the numerator of the equation $\frac{BHCO_3}{CO_2}$, which, due to renal compensation, accompanies any chronic increase in CO_2 appears all important in these phenomena. There is sufficient accumulated proof of this fact in clinical experience. Rahn and Otis[7] found that acute exposure to low alveolar P_{O_2} produced hyperventilation with a decrease in Pa_{CO_2} which disappeared when normal alveolar P_{O_2} was recovered; but after some time of sojourn at high altitude the inhalation of O_2 for brief periods did not change ventilation.

The experiments of Brown[17] of increased sensitivity after overbreathing normal subjects in a respirator and of Schäfer[18] after prolonged exposure of normal subjects to 3 per cent CO_2, in which ventilatory response falls, add further weight to this interpretation.

In all these cases, the bicarbonates suffer opposite changes and it is very difficult to dissociate the effects of total CO_2 change from those of modifications in $\frac{BHCO_3}{CO_2}$ relationship.

Tenney[6] found that in emphysema there was an inverse relationship between sensitivity to CO_2 as measured by the slope of stimulus-response curve and CO_2 content of blood. In keeping with this, we studied a patient with initial Pa_{CO_2} of 35 mm. Hg, $BHCO_3$ of 42.7 vol. per cent, pH of 7.35, Sa_{O_2} of 92 per cent, $\dot{V}_E$ of 6.5 L./M.²/min., and $\dot{V}_A$ of 3.2 L./M.²/min. in metabolic acidosis who did not tolerate 5 per cent CO_2 and had to be studied on 3 per cent CO_2 and showed a 6.7 L. rise in alveolar ventilation per mm. Hg increase in $PaCO_2$. Another patient, an emphysema case (Group 2 of Baldwin, Cournand, and Richards) with initial $PaCO_2$ of 38 mm. Hg, $BHCO_3$ of 56.8 vol. per cent, pH of 7.44, Sa_{O_2} of 81 per cent, $\dot{V}_E$ of 6.4 L./M.²/min., and $\dot{V}_A$ of 3.11 L./M.²/min. showed a response intermediate to that of normal subjects and patients with CO_2 retention (Fig. 2).

The results in normal subjects with 6063 showed some interesting data: the fall in blood bicarbonates and Pa_{CO_2} were present in all cases and their balance was altered in the sense of a decrease in pH.

Nadell[19] described the effects of Diamox in normal subjects and patients with respiratory acidosis and the subsequent fall in arterial Pa_{CO_2}. Although the respiratory variables were not measured, this author thought that lowering of Pa_{CO_2} was secondary to hyperventilation. It is probable that metabolic renal acidosis provoked by the drug stimulates a homeostatic mechanism tending to reinstate a normal pH by way of increased CO_2 elimination. The studies of Galdston[20] have shown that the effects upon CO_2 start primarily through the kidneys, since a blood bicarbonate fall is the first effect in acute experiments, the fall in arterial P_{CO_2} being a later event. The only two ways CO_2 can decrease in the body are: by a lowering in its metabolic production or increase in its excretion by the lungs, since renal excretion is insignificant in comparison.

In our cases CO_2 production showed a small decrease in normal subjects in keeping with the observation of Galdston. The mean difference of 12 c.c. is not significant ($p = 0.05$); on the other hand, alveolar ventilation showed some increase in all cases except one (D.B.) though in this latter case Pa_{CO_2} fell too. The finding of a higher ventilation in the normal subjects in face of a lower arterial P_{CO_2} can only be interpreted in the sense of a lower threshold of the respiratory center for CO_2, produced either by reflex or direct effect of Diamox upon the center. Similar results have been reported lately by Galdston.[20] Sensitivity to CO_2 as expressed by a stimulus-response curve relating ventilation and arterial P_{CO_2} during inhalation of a CO_2 mixture showed inconstant changes (Table I, Figs. 2 and 7).

We believe that in these cases in which arterial P_{CO_2} is so much lowered, inhalation of a mixture of a higher P_{CO_2} than that present in arterial blood sets a limit for arterial P_{CO_2} which logically cannot be lower than inspired P_{CO_2}, whatever the ventilation may be. In those cases inhalation of a mixture less concentrated would have been advisable but was not tried in the present study.

The effects of 6063 in emphysema were similar to those already presented[16,19,21] with the difference that we found some decrease in arterial P_{CO_2} in relation to that of blood bicarbonates (except in A.S. in acute acidosis). As in normal subjects we feel that the finding of the same ventilation as in the controls with lower Pa_{CO_2} (Fig. 7), as well as higher ventilatory responses to CO_2 with lower figures for Pa_{CO_2}, points to an index of an increase in sensitivity of the respiratory center to CO_2, rather pronounced in some cases (J.S. and J.M.), as well as a decrease in its threshold.

In some cases the increase in $\dot{V}_A$ was small or even reversed (L.G.R.) but it is probable that an instantaneous determination of $\dot{V}_A$ may not, on occasion, be representative of its over-all behavior, and a small increase per minute may be significant over a 24-hour period.

It would be interesting to have more studies on the behavior of the respiratory center analyzed with respect to threshold and sensitivity curves. On that point, Patient E.D. was a good example of a rise in threshold (Pa_{CO_2}: 68 mm. Hg with $\dot{V}_E$: 3.18 L./M.²/min. and $\dot{V}_A$: 1.93 L./M.²/min.); when exposed to CO_2 he showed a very good sensitivity index (for his state of CO_2 retention) of 640 ml./mm. Hg rise in Pa_{CO_2}. This could be interpreted by accepting that his center, though needing a very high Pa_{CO_2} to produce normal $\dot{V}_A$, was from thereon in a better condition to respond to increases in Pa_{CO_2}. The same behavior was observed after Diamox (Tables III and IV).

The study of the patients breathing different gas mixtures brought out certain considerations

valuable from a physiologic and perhaps therapeutic standpoint. The respiratory depression produced by "pure" O_2 inhalation in patients with emphysema and CO_2 retention, which is accompanied by increased arterial P_{CO_2} with cerebral depression, coma, and even death,[22,23] is well known. In our patients (see Table VII) breathing O_2, alveolar ventilation was lower than normal (in 23 to 53 per cent) in spite of a higher arterial P_{CO_2} (from 7.5 to 17 mm. Hg). This fact can be taken as evidence of a transitory decrease in the sensitivity of the respiratory center produced by O_2 inhalation. While all these facts are well known there is still lack of knowledge regarding the real cause of ths somnolence and coma seen in these cases. Dripps[24] showed that in normal subjects inhalation of 10 per cent CO_2 could induce mental depression; otherwise the narcotic properties of CO_2 in 20 per cent concentration are well known. On the other hand, Comroe[23] in two cases with high arterial P_{CO_2} could not induce sleep by 10 per cent CO_2 inhalation during a 5-minute interval in spite of an acute increase of arterial P_{CO_2}. Cerebral vasoconstriction by high arterial P_{CO_2} has been denied by Kety while there is not sufficient proof of the possibility of enzymatic mechanisms damage by high P_{O_2}.

It has been suggested that the relief of anoxemia by O_2 breathing in cases of acutely ill emphysema patients with respiratory intercurrent complications could be accomplished with less risk if CO_2 was added concomitantly. A mixture of 5 per cent CO_2 in O_2 has been proposed for this purpose.[25] Boutourline-Young[8] tried it in two patients with acute respiratory acidosis, obtaining decrease in ventilation as compared with that obtained with room air. We have observed four cases in which the ventilation decreased while breathing O_2 and in which a mixture of 5 per cent CO_2 in oxygen produced a ventilation similar to that while breathing room air. Arterial P_{CO_2} was measured in only one case and found to be 5.5 mm. Hg higher than with O_2 (Table VII). The results in this case seem to illustrate the pattern of ventilatory control in relation to arterial P_{O_2} and P_{CO_2}. At the beginning this patient had a low P_{O_2} and high P_{CO_2} with a ventilation of 4.7 L./M.²/min. Carbon dioxide breathing markedly increased P_{aCO_2} and to a lesser degree S_{aO_2}, provoking an increase in ventilation. Breathing "pure" oxygen the ventilation decreased by 27 per cent; keeping the S_{aO_2} almost at the same level but increasing the P_{aCO_2}, the ventilation surpassed slightly the control figure in spite of a higher P_{aCO_2}. We have seen patients in whom O_2 breathing provoked somnolence which was relieved by the mixture of 5 per cent CO_2 in O_2, although in this case the arterial P_{CO_2} was higher. This response seems to correlate with Comroe's[23] finding of somnolence in patients breathing O_2 with arterial P_{CO_2} of 52 and 77 mm. Hg, while other patients did not develop that symptom with arterial P_{CO_2} of 92 and 120 mm. Hg, obtained breathing 10 per cent CO_2, with the advantage, for our cases, that these facts are shown in the same patients.

From the therapeutic standpoint we must not forget that if hypoxia is relieved by breathing the CO_2-O_2 mixture, arterial P_{CO_2} is substantially increased as well, though somnolence is not induced during the short periods of exposure. We have used this mixture intermittently in severely ill patients in a state of drowsiness or coma (aggravated by O_2 breathing) without increasing mental depression. It goes without saying that if efficient mechanical means for providing hyperventilation are available they are to be preferred in every case.[8,26]

Contrary to the results published by Galdston, in our experience (Table VIII) the ventilatory depression provoked by O_2 inhalation in emphysema patients decreased after use of Diamox. In all cases this was associated with higher initial (though not normal) O_2 saturation of arterial blood and lower bicarbonates, P_{aCO_2} and pH (except for this last variable in A.S., in acute respiratory acidosis). In the case of E.D. (Table VIII) periodic breathing was apparent while breathing "pure" O_2 in the control state and not after Diamox. We believe that these effects are opposed to the idea of Barach[22] that O_2 narcosis is secondary to acute increase in acidosis brought about by CO_2 increase without time for renal adjustment of bicarbonates, since in our cases pH is lower after Diamox and falls more with O_2 breathing (except A.S., already mentioned). On the other hand it is possible that lower initial P_{aCO_2} or an improvement of the respiratory center may be instrumental.

TREATMENT OF ACUTE AND CHRONIC RESPIRATORY ACIDOSIS

We have been concerned whether acetazoleamide administration was advisable in treatment of acute respiratory acidosis superimposed on chronic acido-

sis and brought about by a respiratory intercurrent complication. A fundamental point is whether a ventilatory response would be possible in the mechanical state of the patient's lung and/or the respiratory center. It seems impossible to judge this in advance, but a cautious trial of CO_2 mixture may give a clue in this sense. If a ventilatory response were not obtained by Diamox the danger of intensifying an already present and marked acidosis cannot be overemphasized. On the other hand, if we could provide the means to control the hypoventilation mechanically or at least decrease the resistance of breathing by the use of bronchodilators and alleviation of lung congestion in cases of uncompensated cor pulmonale, the use of Diamox might be valuable.

In chronic acidosis we have seen the development of more alertness during the administration of Diamox, which we attribute to decrease in arterial P_{CO_2}. Even though this effect is self-limited, it can be maintained with prolonged therapy. Its use in those cases may provide a means of stopping the natural development of the biochemical events of disease, such as CO_2 retention → respiratory center acclimatization → decreased sensitivity to CO_2 → increased retention.

CONCLUSIONS

1. Our studies confirm the fact that patients with emphysema and cor pulmonale in the stage of CO_2 retention show a lower than normal ventilatory response to CO_2 inhalation.

2. The threshold of the respiratory center to CO_2 is increased in those patients as their basal alveolar ventilation is normal or low in spite of an increase in arterial P_{CO_2}.

3. Sensitivity of the respiratory center to CO_2, as measured by a stimulus-response curve, is decreased in direct relationship with initial arterial P_{CO_2}.

4. Ventilatory responses to "pure" O_2 and CO_2 in oxygen are interpreted in the following manner: O_2 breathing provokes hypoventilation due to the quick increase in arterial P_{O_2} and in spite of increase in arterial P_{CO_2}; when CO_2 is added (CO_2-O_2 mixture) a higher arterial P_{CO_2} is obtained and O_2 depressor effects are unbalanced, resulting in a ventilation approaching the patient's initial one.

5. The abnormal response to CO_2 inhalation is not due to any of the following: (a) mechanical limitations, (b) increase in buffer power of blood, or (c) reduction by CO_2 inhalation of the anoxia drive upon the respiratory center.

6. The administration of acetazoleamide (6063) induces a variable decrease in arterial $BHCO_3$, pH, and P_{CO_2} in normal subjects or emphysema patients. In these conditions the threshold of the respiratory center to CO_2 seems lower, since ventilation is higher than control in normal persons or emphysema patients, in spite of a lower arterial P_{CO_2}. Sensitivity studies show variable results.

7. As $BHCO_3$ and total CO_2 descend together, it is impossible to deduce on the basis of these studies if the results on the center are due to a decrease in $BHCO_3$ or in total CO_2 with "acclimatization" to a lower level.

8. Acetazoleamide seems to diminish the respiratory depression produced in emphysema patients by "pure" O_2 inhalation.

9. Acetazoleamide should be used cautiously in patients in acute respiratory acidosis since, if hyperventilation is not produced, it will result in a more severe acidosis.

10. The use of acetazoleamide in chronic respiratory acidosis seems a valuable adjunct to the usual therapy.

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THE EFFECTS OF RESPIRATION ON THE ELECTROCARDIOGRAM IN RELATION TO DIFFERENCES IN RIGHT AND LEFT VENTRICULAR STROKE VOLUME

A Clinical Observation

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A COMMON and often repeated idea is that the electrocardiogram varies due to changes in cardiac position associated with respiration. This simple explanation assumes that the heart becomes more vertical as the diaphragm descends and more horizontal as the diaphragm becomes elevated. This variation has been noted chiefly in Lead III. The variation in this one lead is the basis for the practice of recording Lead III in both inspiration and expiration.

The chief difficulty with the concept of change in cardiac position secondary to diaphragmatic excursion is that it is an oversimplification. The mechanisms responsible for the electrocardiographic changes are much more complicated and offer much more clinical information than would be supposed from such a simple theory. The fallacy in assuming simple diaphragmatic excursion as the principal mechanism for ECG changes can be demonstrated easily by routine electrocardiography. The demonstration of more important mechanisms promises to be of value in clinical application and in simple demonstrations of fundamental electrocardiographic principles often approached by more complicated mechanisms.

EFFECT OF RESPIRATION ON THE NORMAL ELECTROCARDIOGRAM

By recording simultaneously Leads I, II, III, and V_2, one has a three dimensional evaluation of electrocardiographic events. On inspiration there is a distinct loss of QRS amplitude. This is not an axis shift. The amplitude decreases in Lead I and in the S wave of Lead III, without any increase in the amplitude in Lead II (Fig. 1). A true vertical shift in electrical axis would cause an increase in QRS amplitude in Lead II in such circumstances. In Lead V_2 there is marked decrease in the amplitude of the S wave, with little or no change in the R-wave amplitude. The change in V_2 prevents assumption of a significant positional change in the transverse plane. The irrefutable observation is that a significant and total reduction in QRS amplitude occurs on inspiration, rather than a simple shift in heart location.

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The changes noted on inspiration are chiefly in the latter half of the QRS cycles, i.e., diminution of the S wave in Lead III and V_2, with decrease of the R wave in Lead I. The electrocardiographic changes often vary markedly with the phase of inspiration. When the heart rate is increased at the onset of inspiration, the loss of S-wave amplitude in Lead V_2 is apt to be most marked (Fig. 1). By breath holding at the height of inspiration, marked slowing of the heart rate occurs. Diminished QRS amplitude is maintained even though the heart rate is slower than prior to the onset of inspiration.

The changes noted in QRS amplitude with respiration are not dependent upon the electrical axis. In the presence of a leftward axis of minus 30 degrees similar findings are present (Fig. 2).

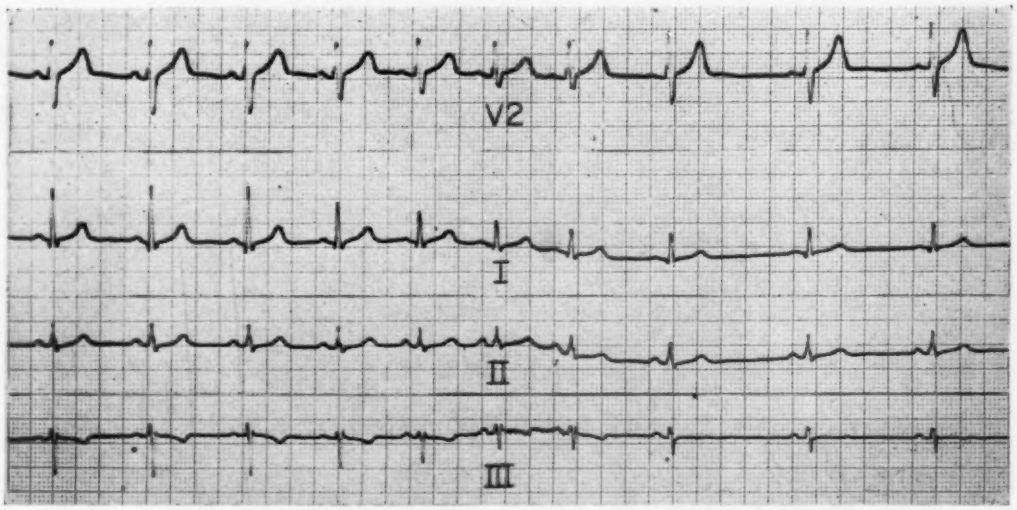


Fig. 1.—This is the simultaneous record of Leads V_2, I, II, and III during the respiratory cycle. The mean QRS axis is 0 degrees. Inspiration begins after the third QRS complex. Immediate reduction in QRS amplitude is noted. The rate increases on inspiration. Note that Lead II shows no appreciable change in QRS amplitude. After the eighth QRS complex the subject holds his breath at the height of inspiration, causing vagal slowing. The S wave in V_2 increases despite maximum lung inflation. (Note that the R wave in V_2 actually increases while holding the breath at full inspiration during the last three QRS complexes.) The QRS amplitude remains small in Leads I, II, and III. The terminal R wave in Lead III disappears in the last three QRS complexes. This loss of the terminal right-hand force is not compatible with the concept of simple vertical (rightward) shift of the heart.

Three dimensional analysis is particularly important in observing the respiratory changes in Lead I with a vertical electrical axis. The terminal S wave of Lead I represents a terminal rightward vector. The simultaneous S wave of Lead V_2 locates the terminal QRS vector posteriorly, as well as rightward. On inspiration the S in Leads I and V_2 is greatly diminished. If one assumed a more vertical heart position on inspiration, the terminal rightward vector would be increased, not diminished (Fig. 3).

The respiratory influence causing decreased QRS amplitude is noted in the presence of a marked terminal rightward vector with posterior spatial orientation (Fig. 4). As in the previous examples, the principal respiratory effects are noted in the last half of the QRS cycle.

There are exceptions to every observation, however, as is often the case in a biologic event. Rarely is a paradoxical response noted on respiration (Fig. 5). The QRS amplitude may increase while holding the breath in deep inspiration. When this occurs the S wave in Lead V_2 will increase in amplitude. The increased amplitude is associated with marked slowing of the heart rate. As soon as the initial peak of vagal slowing is diminished, there is a second reduction of the S-wave amplitude in Lead V_2. The insulating effect of the inflated lung is relatively unchanged throughout these changes at full inspiration.

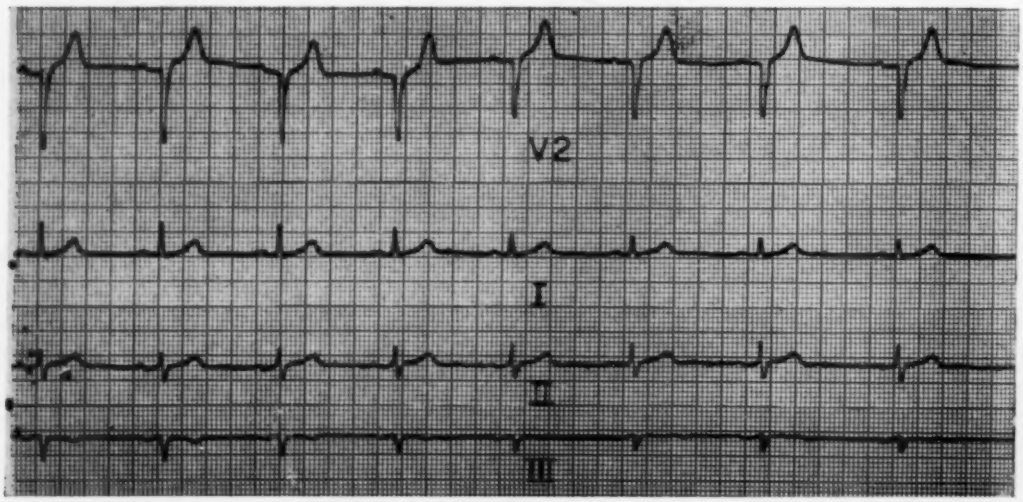


Fig. 2.—Inspiration begins after the first QRS complex. The mean QRS axis is minus 30 degrees. There is a decrease in the magnitude of the terminal 0.04 sec. QRS vector. The most marked change is in the S wave of V_2.

The observations noted above in the normal electrocardiogram during the respiratory cycle permit certain factual observations:

1. The changes observed in the electrocardiogram with respiration cannot be explained on the basis of a simple shift in the anatomic position of the heart.
2. There is a decrease in the spatial magnitude of the terminal QRS vector on inspiration.
3. The change in magnitude of the terminal spatial QRS vector cannot be attributed to the insulating effect of the inflated lung, as evidenced by the following:

a. There is a tendency to increase the QRS amplitude while holding the breath in fixed inspiration.

b. The occasional paradoxical response with increased QRS amplitude occurs while holding the breath at full inspiration with maximum inflation of the lungs.

c. There is selective diminution of the terminal spatial QRS forces, with little or no effect on the magnitude of the initial spatial QRS vector once maximum inspiration has been achieved.

4. The changes noted in QRS magnitude cannot be attributed to differences in vagal and sympathetic influences on basic electrical events. Diminished

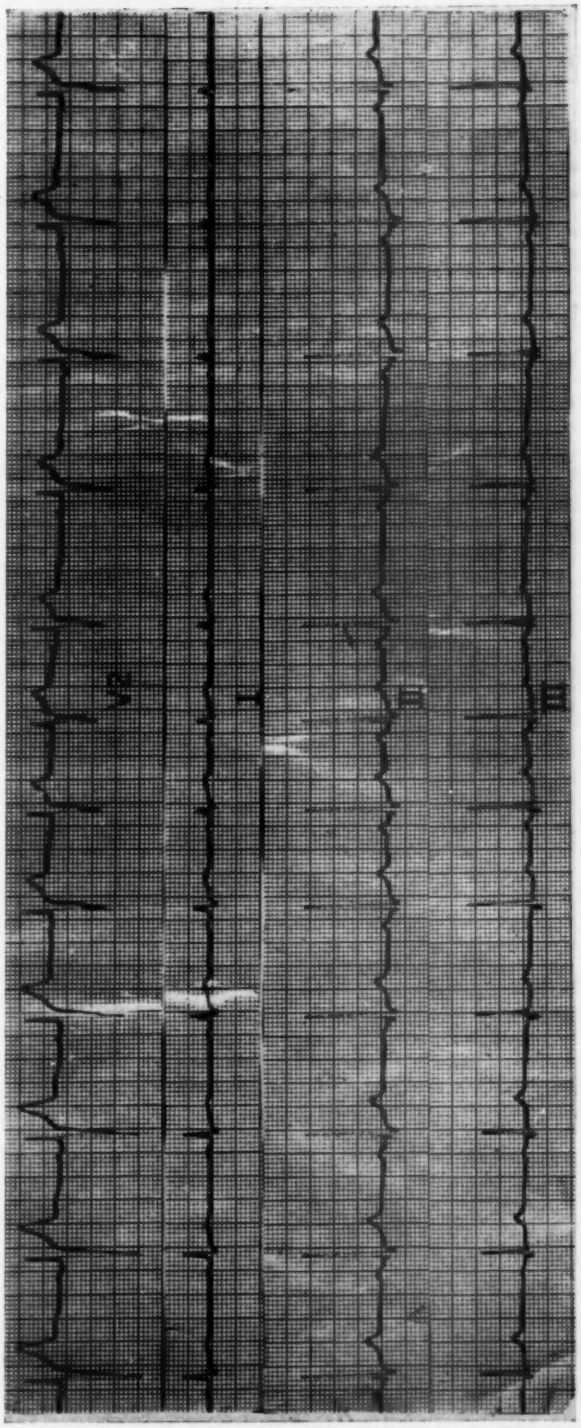


Fig. 3.—This is a respiratory electrocardiogram with a nearly vertical mean QRS electrical axis. The S wave of Lead V_2 shows a spirogram cycle with decreasing amplitude on inspiration and increasing amplitude while holding inspiration. Lead V_2 may be used as a spirogram in this fashion. The gradual increase in S-wave amplitude while holding maximum inspiration is objective proof that the respiratory effects are not due to insulation by the inflated lung. Note the loss of the S-wave amplitude in Lead I. There is minimal increase in the R-wave amplitude in Lead III.

magnitude is noted while the heart rate is increasing at the onset of inspiration, as well as while holding inspiration, with maximal vagal inhibition causing slowing of the heart rate.

5. There are three distinct phases to the effects of respiration on the electrocardiogram:

a. At the onset of inspiration the heart rate is accelerated. During this phase there may be a decrease in both the initial and terminal spatial QRS forces. The most marked effect is on the magnitude of the terminal spatial QRS vector.

b. By holding the breath at the height of inspiration, marked slowing of the heart rate usually occurs.* At this stage there is some increase in the QRS amplitude toward the preinspiratory character. With marked slowing the QRS amplitude may equal or exceed the preinspiratory QRS amplitude.

c. On expiration after breath holding the terminal spatial QRS vector may increase above the control record on the third to fifth cardiac cycle after expiration.

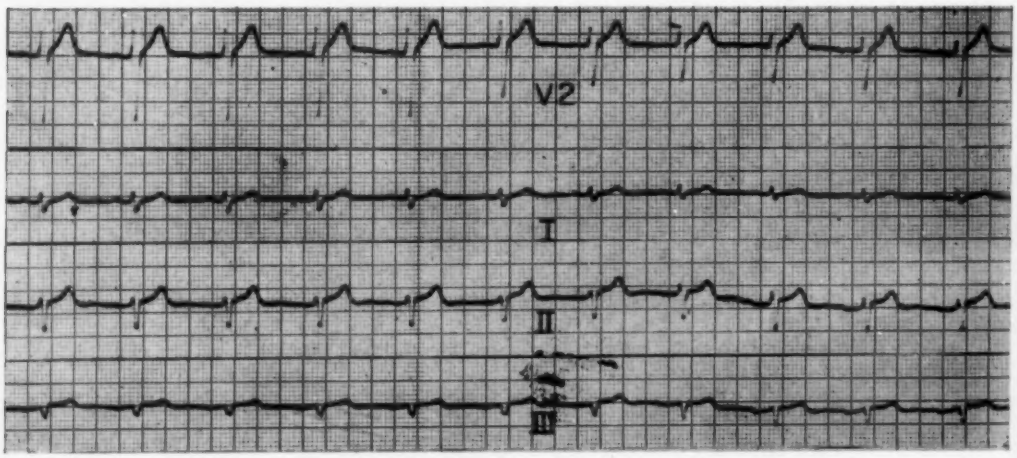


Fig. 4.—Respiratory effects are noted in this example of a mean QRS axis of minus 120 degrees. The terminal QRS vector is directed toward the right shoulder and posterior, causing an S wave in Leads V_2, I, II, and III. The selective changes of the S wave of Lead V_2 are most marked.

The changes noted in the electrocardiogram with respiration correlate with known physiologic differences in filling of the right and left ventricles.[1] On inspiration the right ventricle enlarges and receives more blood, due to increased negative intrathoracic pressure. The left ventricle receives less blood, because the pulmonary vascular bed is expanded and is able to pool a large portion of the blood expelled from the right ventricle. The disproportion between right and left ventricular filling is reversed during expiration. The venous return to the right ventricle is decreased, resulting in decreased volume of the right ventricle. The volume of the pulmonary vascular bed is diminished and the excess blood is expelled into the left ventricle, increasing left ventricular filling. When the changes in pulse pressure can be noted at the bedside, it is termed a paradoxical pulse.

*The Valsalva maneuver is avoided and the breath is held with as little muscular effort as possible.

Filling of the ventricles also depends upon cardiac rate. The increased rate at the onset of inspiration may diminish the stroke volume of both ventricles, and selectively that of the left ventricle. Slowing of the rate, while breath holding in inspiration, increases the diastolic filling period and tends to increase the stroke volume.

Respiration has been noted to affect primarily the terminal half of the QRS cycle. This portion of ventricular excitation is normally limited to activity in the left ventricle. As the left ventricular stroke volume decreases, the terminal QRS spatial vector decreases. When cardiac rate is accelerated on inspiration, a minimal decrease in the initial spatial QRS-vector magnitude may occur. The three phases of electrocardiographic changes noted with respiration correspond with expected physiologic changes in stroke volume. The paradoxical electrocardiographic response with increased QRS amplitude occurs with marked cardiac slowing and time for increased diastolic filling.

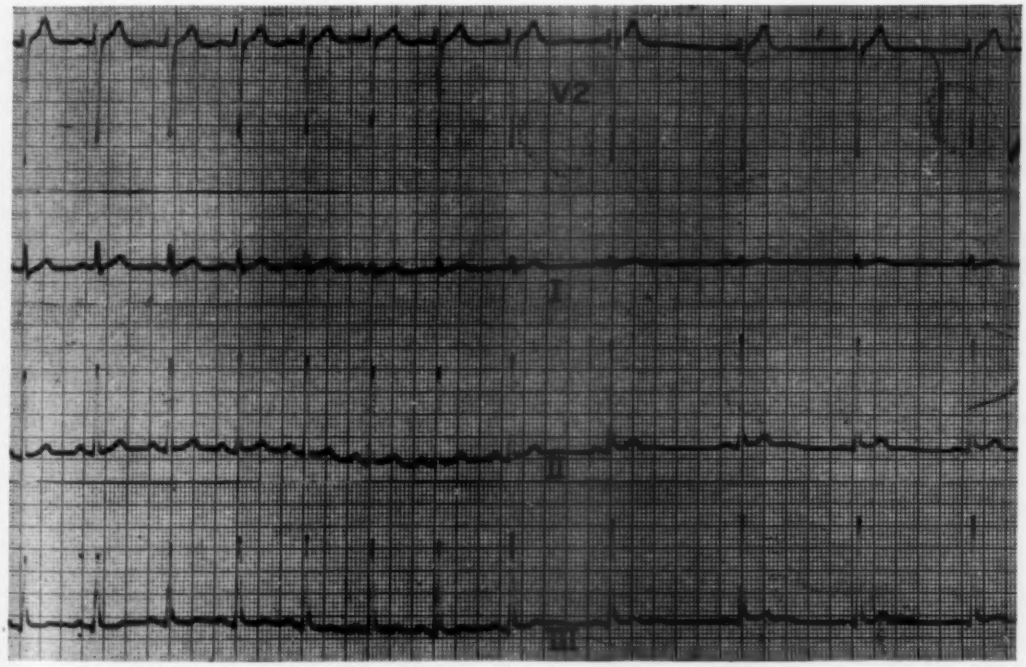
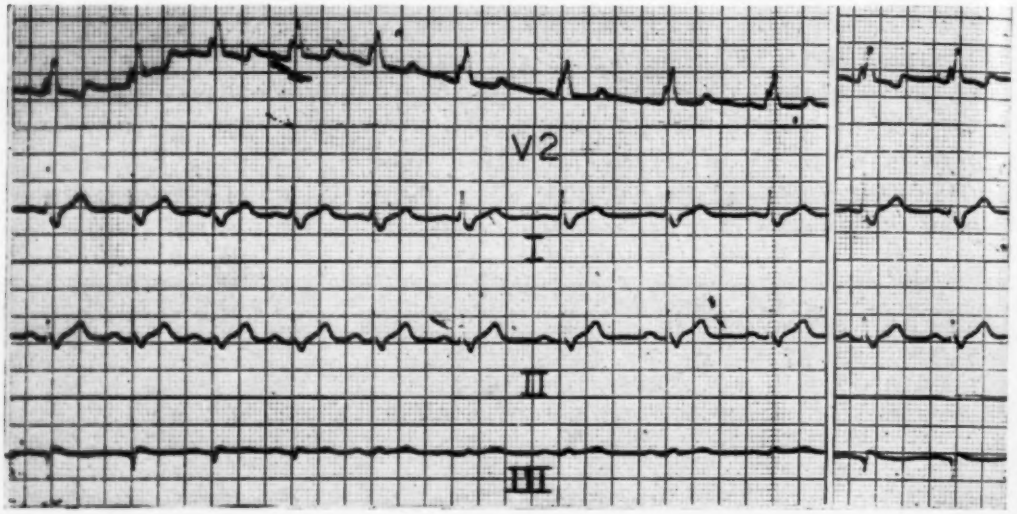


Fig. 5.—This is an example of a paradoxical response to inspiration. The first QRS complex is the end of normal expiration. As inspiration begins the heart rate increases and there is progressive decrease in the amplitude of the S wave in V_2. After the sixth cycle the breath is held in deep inspiration. The ninth and tenth QRS cycles are markedly increased in amplitude and the heart rate is only half its inspiratory rate. With inspiration still being held, the peak of vagal inhibition passes and the rate increases; thus, the last QRS complex loses QRS amplitude while lung inflation remains unchanged.

These observations lend considerably more importance to the electrocardiographic findings in respiration than would be supposed from the simple explanation of changes in cardiac position. Considering the very basis of the electrocardiogram, they point up the importance of the volume of the ventricular cones of excitation as a basic factor in QRS amplitude. Clinically, the marked respiratory variations noted suggest that amplitude measurements in the diagnosis of hypertrophy should consider the phase of respiration as well as the cardiac rate.

The importance of the volume of the ventricles in relation to QRS amplitude has been noted in other clinical situations. The increase in rate after exercise is associated with significant decrease in QRS amplitude in certain individuals.[2] Premature nodal contractions with short diastolic filling periods are associated often with decreased QRS amplitude. The cycle succeeding the prematurity may show significant increased QRS amplitude.[2]



A. *B.*

Fig. 6.—This is an example of right bundle branch block during respiration (*A*, Inspiration; *B*, Expiration). Inspiration begins after the first QRS complex. There is a slight increase in the R wave at V_2. The notching is greatly diminished. Considering the sequence of ventricular excitation in right bundle branch block, the notch corresponds to completion of a confluent cone of excitation in the left ventricle. Its decrease corresponds to a decrease in left ventricular volume. On expiration (*B*) the notch returns. The initial R wave in Lead I and the Q wave in Lead III (left ventricle) lose amplitude on inspiration. The terminal S wave in Leads I and II with the terminal R wave in Lead III (right ventricle) remain prominent.

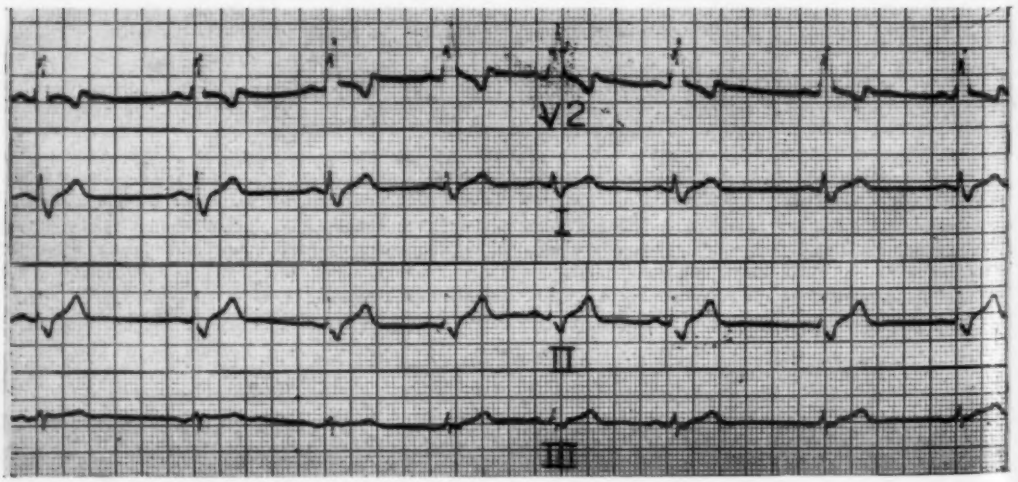


Fig. 7.—The most striking finding in this example of RBBB is the terminal increase in the R wave (right ventricle) in V_2 at the height of inspiration.

In passing, it is interesting to note that ballistocardiographic enthusiasts often cite the supposed ability of the BCG to detect changes in right and left ventricular ejection during the respiratory cycle, in contrast to the electrocardiogram. It seems that the electrocardiogram can be used in a similar fashion if one gives due regard to changes noted during the respiratory cycle.

RESPIRATORY ELECTROCARDIOGRAPHIC CHANGES IN THE PRESENCE OF CONDUCTION DEFECTS

To further substantiate the relation of right and left ventricular stroke volume to QRS amplitude, examples of right bundle branch block, left bundle branch block, and $S_1S_2S_3$ conduction were evaluated. This provided a means of isolating the effects of the right and left ventricular excitation periods during respiration.

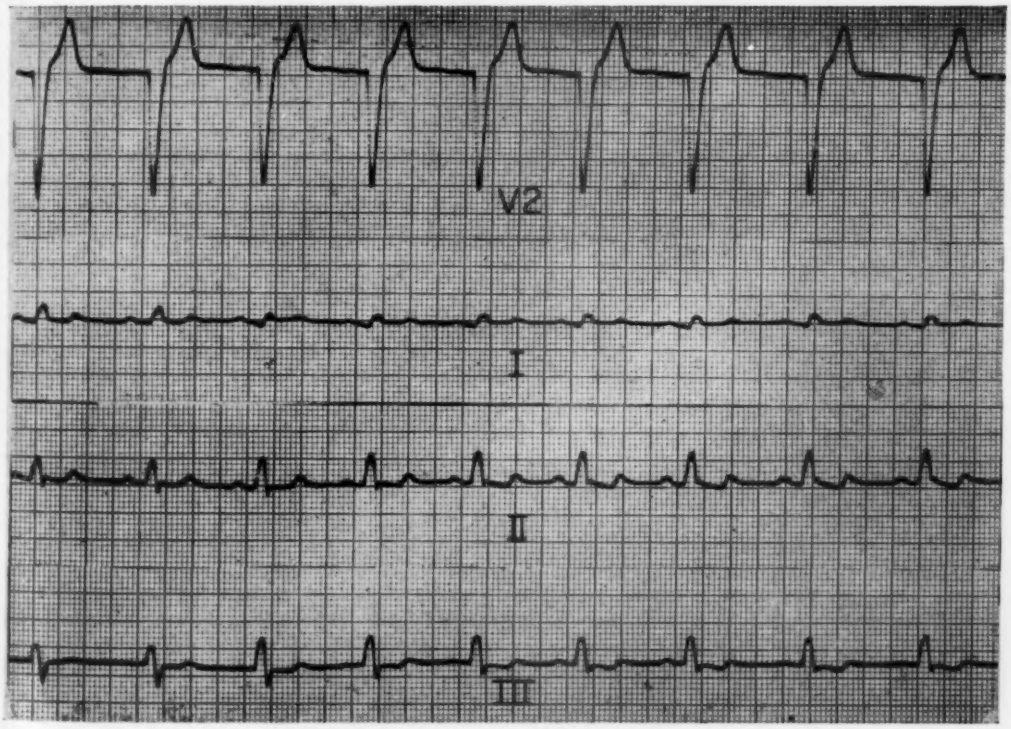


Fig. 8.—This is an example of left bundle branch block and the effects of respiration. Inspiration begins after the first QRS complex. Note the sharp Q wave in Lead I in the third QRS complex, the decrease in the S wave in V_2, and the progressive loss of amplitude of the R wave in Lead I, and of the S wave in Leads II and III. Lead V_2 is recorded at half standard.

Right Bundle Branch Block.—In the presence of right bundle branch block the left ventricle occupies the early part of ventricular excitation and the right ventricle occupies the latter part of excitation. Since the right ventricular volume is increased on inspiration, the terminal R wave in V_2 should be unchanged or increased in amplitude with inspiration, in contrast to a decrease in S-wave

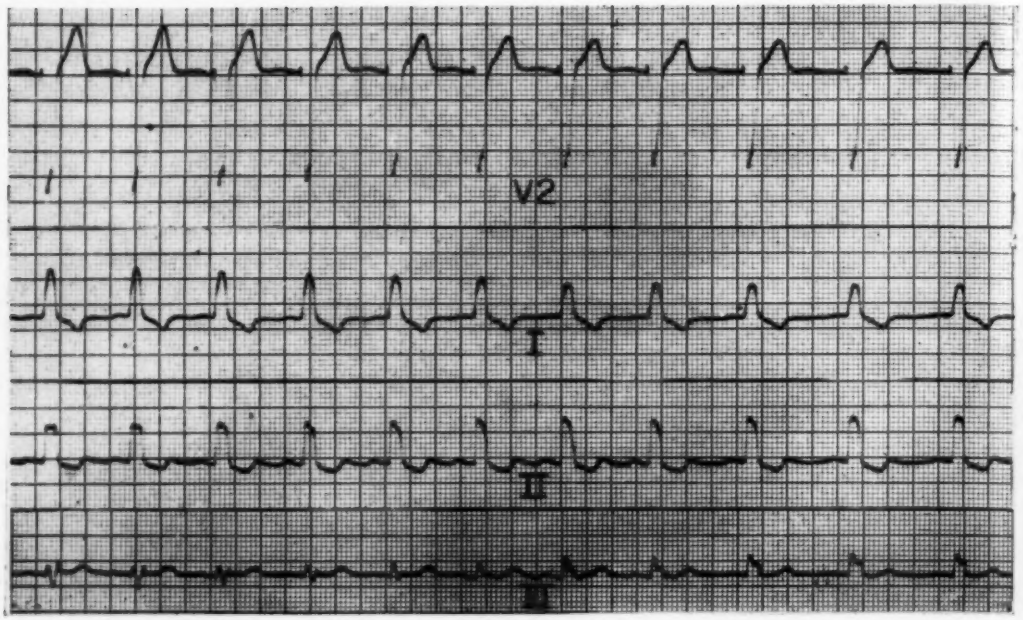


Fig. 9.—The interesting findings in this example of LBBB on inspiration is the loss of S-wave amplitude in V_2 and the change in QRS configuration in Lead II. Note that the plateau effect in Lead II is abolished by increasing the amplitude of the initial R upstroke (right ventricle). This record is thought clinically to have resulted from a myocardial infarction.

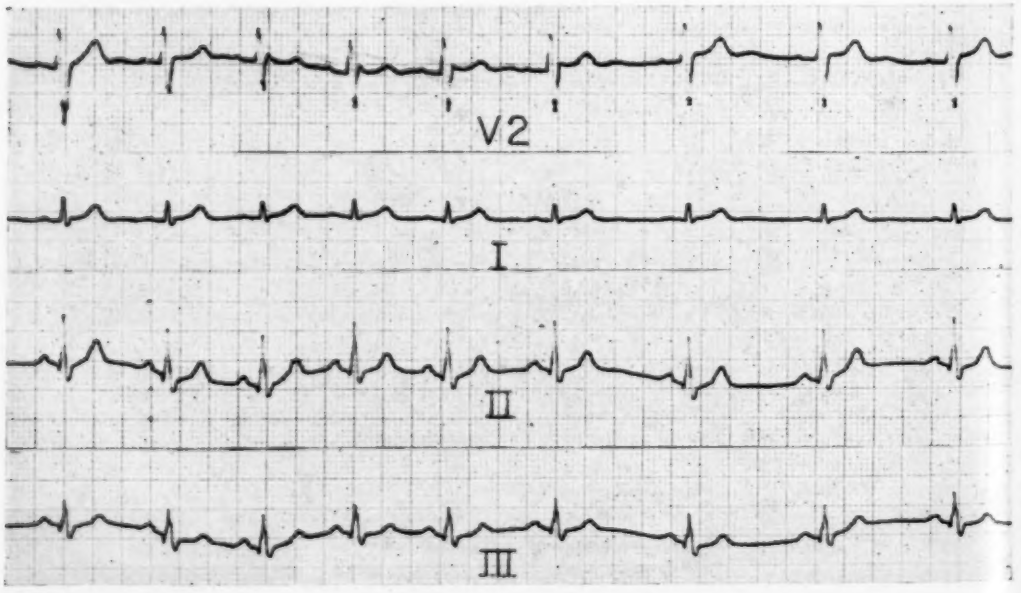


Fig. 10.—This example of an $S_1S_2S_3$ conduction shows persistence of the terminal S wave on inspiration, the appearance of a distinct R′ wave at V_2, and the customary changes of the S wave in V_2.

amplitude seen in the normal electrocardiogram. The electrocardiogram does behave in this manner (Figs. 6 and 7). There is a decrease in magnitude of the initial spatial QRS vector (left ventricle) and an increase in the terminal R wave at V_2. Subtle variations in QRS configuration are noted also. The increase in the R wave in V_2 again emphasizes that the amplitude changes of respiration are not due to insulation by the inflated lung.

Left Bundle Branch Block.—When left bundle branch block is present, the right ventricle occupies the initial events of excitation and the left ventricle occupies the terminal events of excitation. Increase in right ventricular volume on inspiration is associated with an increase in magnitude of the initial spatial QRS vector (right ventricle) and a more rightward spatial orientation. A Q wave may be created in Lead I, due to the increased rightward orientation of the right ventricular vector. The initial R wave in Leads II and III also may increase (Fig. 8). The terminal spatial QRS vector loses magnitude, as evidenced by a sharp decrease in the S wave in Lead V_2 and the R wave in Lead I. Other subtle variations are sometimes noted in the QRS configuration (Fig. 9).

$S_1S_2S_3$ Conduction.—Theoretically, the terminal event of a true $S_1S_2S_3$-conduction defect is due to terminal activation of muscle areas near the tricuspid or pulmonary orifices. Excitation of such an area should be affected very little by respiration. On inspiration the terminal S wave persists (Fig. 10). By diminishing the left ventricular effects, the terminal events may be sharpened, e.g., an R′ wave may appear at V_2.

SUMMARY

The changes noted in the electrocardiogram during different phases of respiration can be correlated with expected differences in stroke volume of the right and left ventricle. The changes are not due to a simple shift in anatomic position of the heart, lung inflation, or autonomic nervous control. By utilizing the difference in sequence of excitation in normal conduction, right bundle branch block, and left bundle branch block, the relationship of electrocardiographic changes to stroke volume is apparent.

The marked changes in QRS amplitude due to the phase of respiration and cardiac rate impose another variable in the usual methods of measuring QRS amplitude in relation to hypertrophy.

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CONFUSION OF TRICUSPID INCOMPETENCE WITH MITRAL INSUFFICIENCY—A PITFALL IN THE SELECTION OF PATIENTS FOR MITRAL SURGERY

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RECENTLY, we observed a number of patients who were initially denied surgery for mitral stenosis because they were thought to have associated mitral insufficiency. However, after careful re-evaluation, operation was subsequently performed and severe stenosis of the mitral valve with little or no insufficiency was discovered. Mitral insufficiency had been diagnosed erroneously because of the presence of a moderately loud apical systolic murmur. Actually, it was the murmur of tricuspid incompetence confused with that of mitral insufficiency. These patients represent an important group of cardiacs who are often denied surgical relief of incapacitating mitral stenosis when they could be helped.

Mitral Insufficiency.—It is generally agreed that severe mitral insufficiency associated with mitral stenosis is a contraindication to valvuloplasty.[1-7] However, it has become apparent that some patients who could be benefited are denied surgery because of the erroneous diagnosis of mitral insufficiency. These errors in proper case selection occur because detection of mitral insufficiency in the presence of stenosis is often difficult. Even the surgeon's digital appreciation of the degree of insufficiency may be occasionally misleading.[2,5,8] In detecting significant associated mitral insufficiency, a combination of clinical criteria seems to achieve the greatest percentage of correct diagnoses. These are (1) a large dynamic left ventricle as evidenced by physical examination, the electrocardiogram, or radiologic examination, (2) an unusually large (giant) left atrium, and (3) a loud apical systolic murmur.[1-10]

The loud systolic murmur is the most important single clinical criterion for the diagnosis of mitral insufficiency. A Grade 3 or more (on the basis of 1 to 6) high-pitched apical systolic murmur usually means significant mitral insufficiency.[2,5,6,8-11] Some stress the pansystolic duration of the murmur rather than its intensity.[12] The murmur characteristically diminishes in intensity on deep inspiration and is usually transmitted best toward the left axilla and pos-

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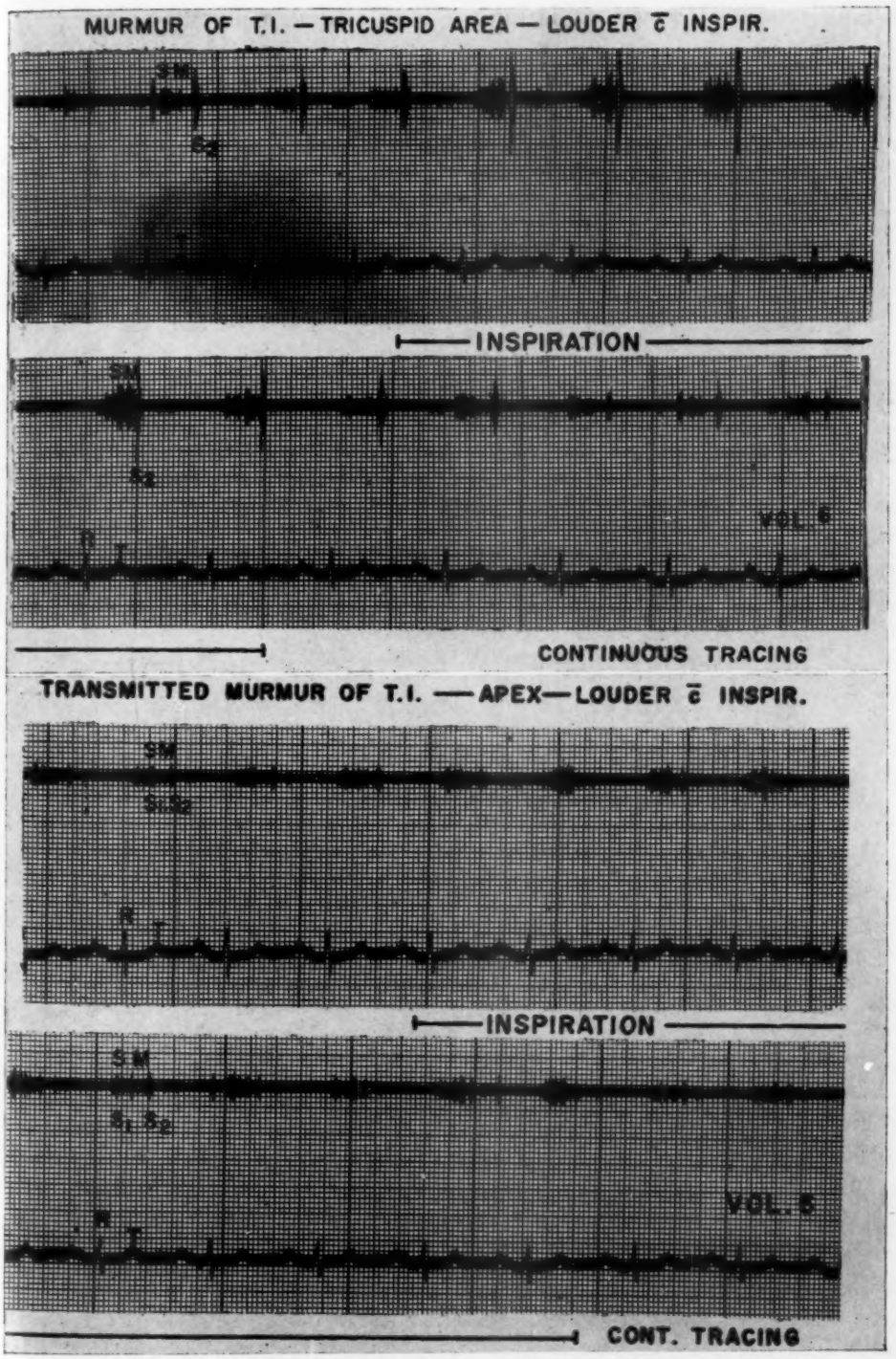


Fig. 1.—26-year-old man with rheumatic heart disease, active carditis, severe mitral stenosis and moderate insufficiency. He had advanced congestive failure with hepatosplenomegaly, ascites, anasarca, and typical tricuspid venous pulses. Diagnosis confirmed at autopsy. *A*, Tricuspid area. Grade 3 harsh systolic murmur (*SM*) became musical in quality and 2 grades louder on inspiration. Second sound (S_2) also became louder. *B*, Mitral area. Systolic murmur (*SM*) became still louder with inspiration.

terior lung base. However, it is known that although a loud apical systolic murmur may be heard, significant insufficiency of the mitral valve may not be demonstrated either at surgery or post-mortem.[5,11] Much less frequently, considerable pathologic mitral insufficiency has been demonstrated where a loud systolic murmur had not been described on physical examination.

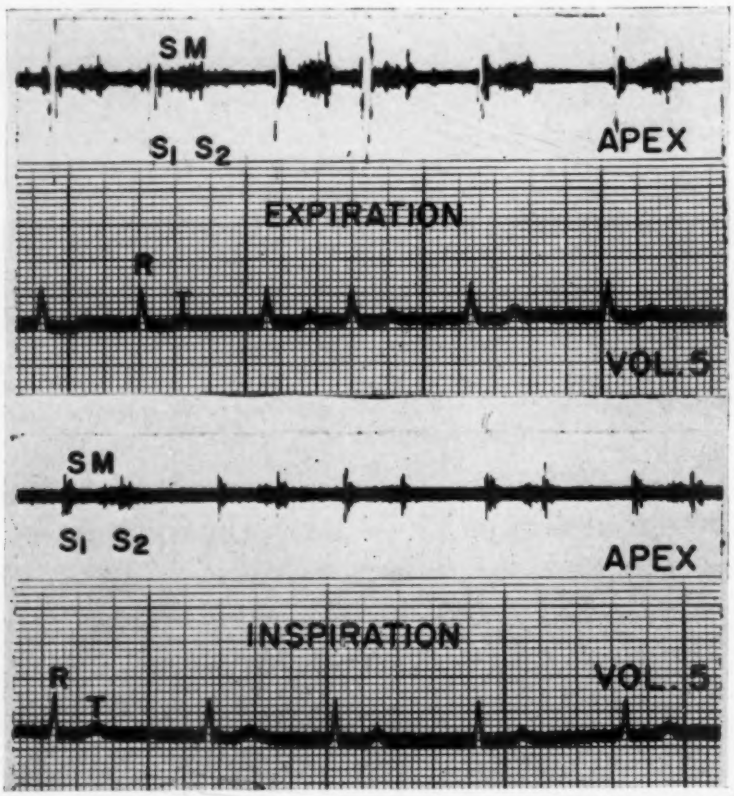
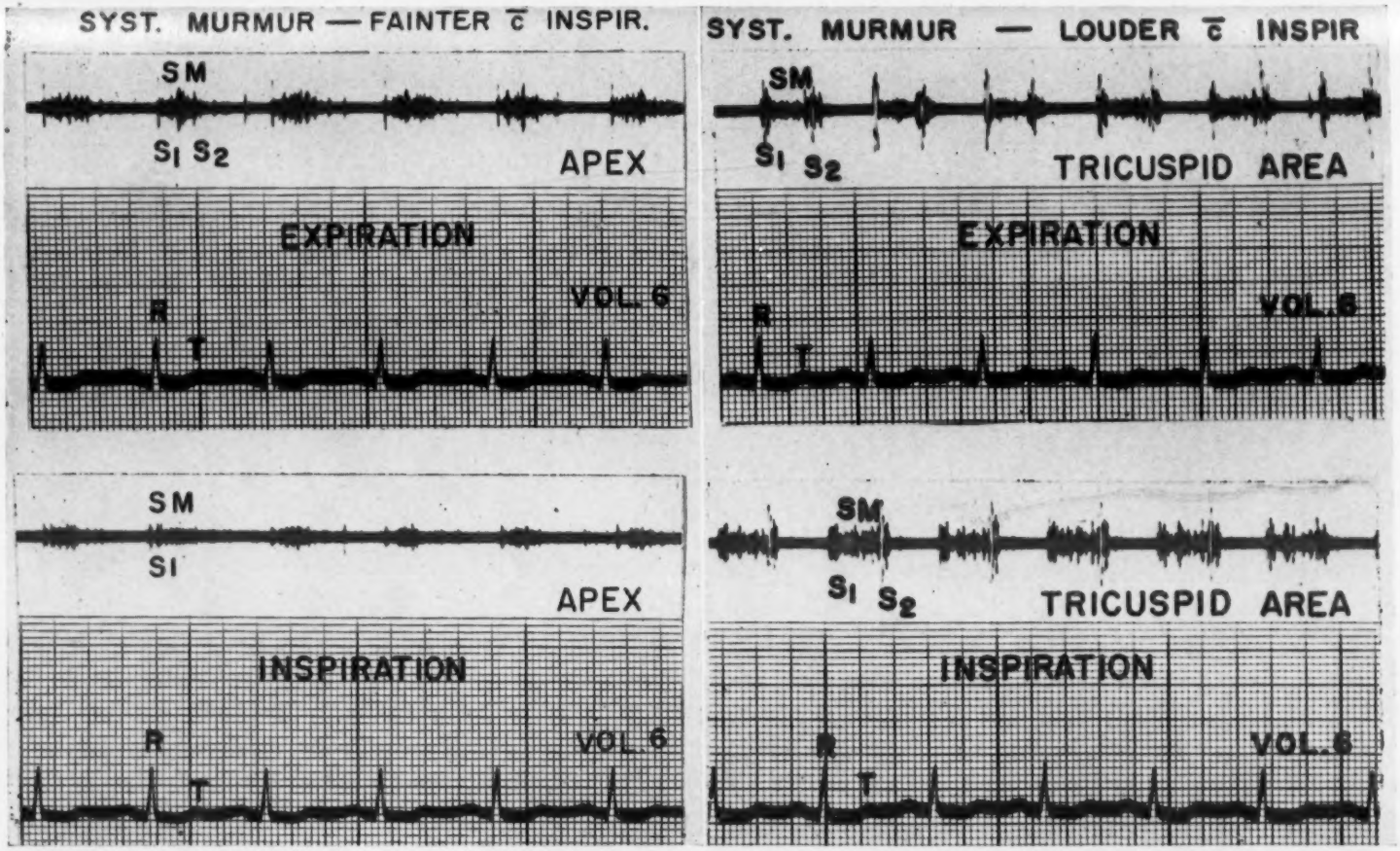


Fig. 2.—24-year-old man with mitral stenosis and insufficiency. No evidence of heart failure clinically. Systolic murmur (*SM*) Grade 4 at apex, transmitted to axillary line and left lung base. Note decrease in murmur and heart sounds with inspiration.

A loud apical systolic murmur in itself is not a contraindication to valvuloplasty in an otherwise suitable candidate.[3,5,7] In many instances such a murmur will prove to be the transmitted murmur of tricuspid incompetence. This was illustrated by a 46-year-old lady who was observed 6 years ago. She was incapacitated with rheumatic mitral disease that was presumed to be predominant mitral insufficiency because of Grade 5 apical systolic murmur. Operation was performed with the intention of correcting the insufficiency, but a tight mitral stenosis with no insufficiency was present. In retrospect, it is probable that tricuspid incompetence was masquerading as mitral insufficiency in this patient. Confusion of the murmur of tricuspid incompetence with that of mitral insufficiency has been noted by others.[11,13-17]

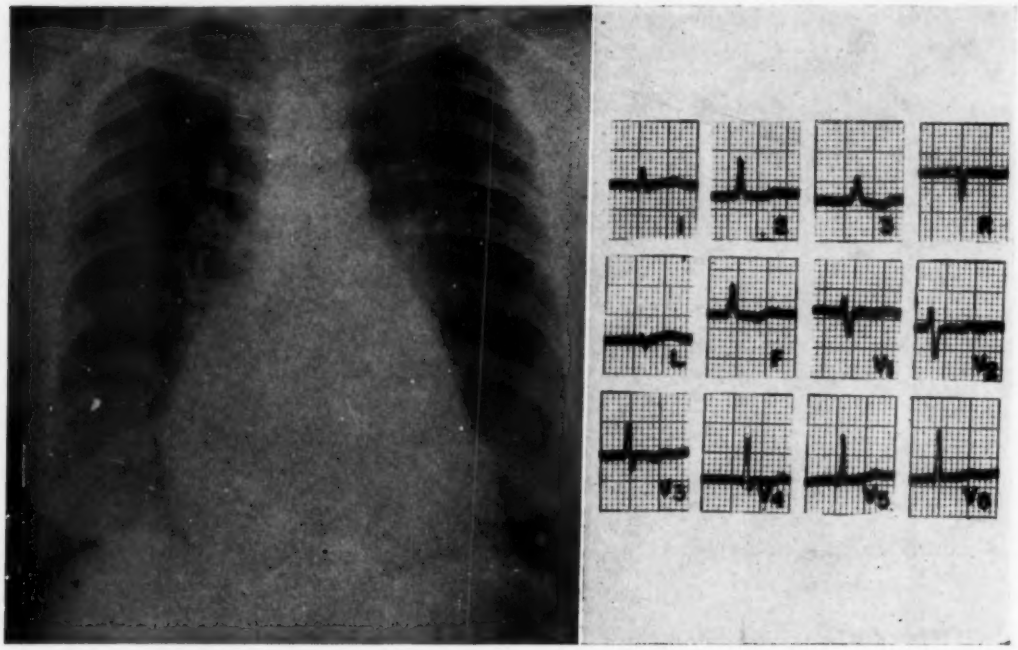
Tricuspid Incompetence.—Functional tricuspid incompetence is not uncommon in rheumatic heart disease with mitral stenosis.[6,17-20] Organic tricuspid



A. *B.*

Fig. 3.—Systolic murmur in 30-year-old woman with surgically proved mitral insufficiency, plus clinical evidence of tricuspid incompetence. *A*, Mitral area. Grade 4 blowing systolic murmur (*SM*) decreased on inspiration. *B*, Tricuspid area. Systolic murmur (*SM*) became louder and higher pitched on inspiration. Murmurs of tricuspid incompetence and mitral insufficiency can be differentiated in this particular patient.

insufficiency is less common.[18] Pathologic evidence of tricuspid incompetence at autopsy or physiologic evidence of it at cardiac catheterization is found more often than the diagnosis is made clinically.[17,19,20] A classical clinical picture with pulsating veins and liver and severe right heart failure may not be present in spite of typical right atrial pressure curves at cardiac catheterization.[17]



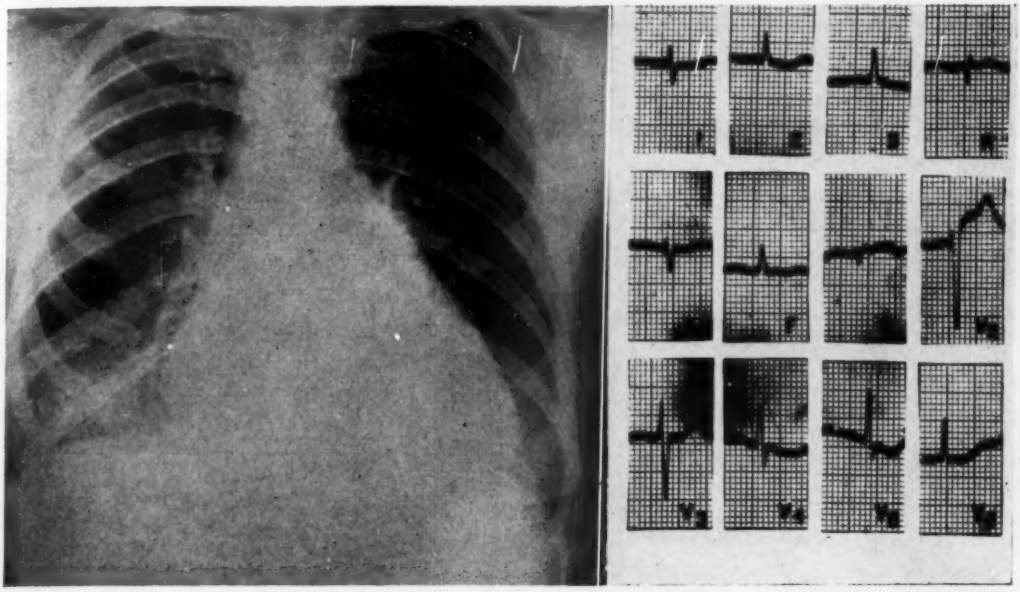
A. *B.*

Fig. 4.—57-year-old woman with rheumatic heart disease, surgically proved tight mitral stenosis, tricuspid incompetence, and congestive heart failure. *A*, Enlargement of both atria, right ventricle, and pulmonary artery. *B*, Atrial fibrillation and digitalis effect.

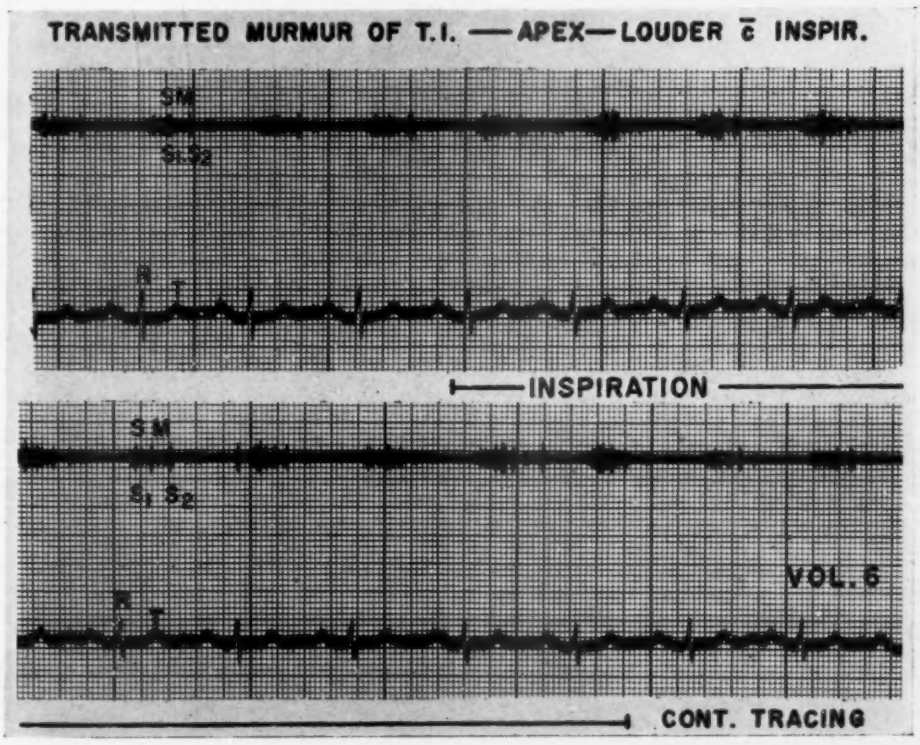
The murmur of tricuspid incompetence varies considerably. It may be soft, high-pitched, musical, or even harsh. In contrast to the murmur of mitral insufficiency, it is often more "superficial," seeming close to the ear. It is heard best over the xiphoid area and along the lower left sternal border, but can be transmitted toward the apex, where it may be confused with mitral insufficiency[11,13,20] (Figs. 1, 6, 7, 8).

The classical murmur of tricuspid incompetence is frequently inconstant and may vary in intensity from day to day.[17,20] As a rule, it gets louder following exercise. Occasionally, it appears with the onset of atrial fibrillation and disappears with normal sinus rhythm.[20] It is generally loudest following long diastolic pauses, varies with position, and may disappear with improvement in the degree of cardiac compensation.[20]

The murmur of tricuspid incompetence becomes louder on deep inspiration (Carvallo's sign) (Figs. 1, 5, 6, 7) in contrast to the murmur of mitral insufficiency which becomes fainter[19-21] (Fig. 2). The increase in intensity is most marked during early inspiration, becomes stabilized if the breath is held for a moment,



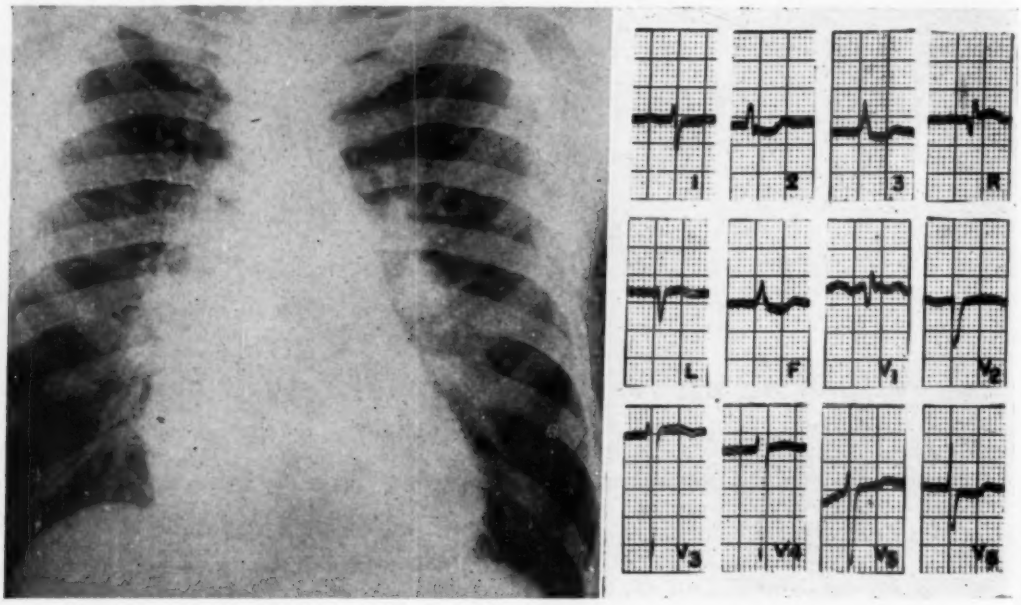
A. *B.*



C.

Fig. 5.—47-year-old woman with rheumatic heart disease, surgically proved tight mitral stenosis, and severe tricuspid insufficiency clinically. *A*, Cardiac enlargement with prominent pulmonary artery segment. On fluoroscopy both atria and right ventricle were very much enlarged. The mitral valve was calcified. *B*, Atrial fibrillation, right axis deviation, and digitalis effect. *C*, Systolic murmur (*SM*) Grade 4, loudest in tricuspid area, but transmitted to the apex. Note increase in intensity with inspiration.

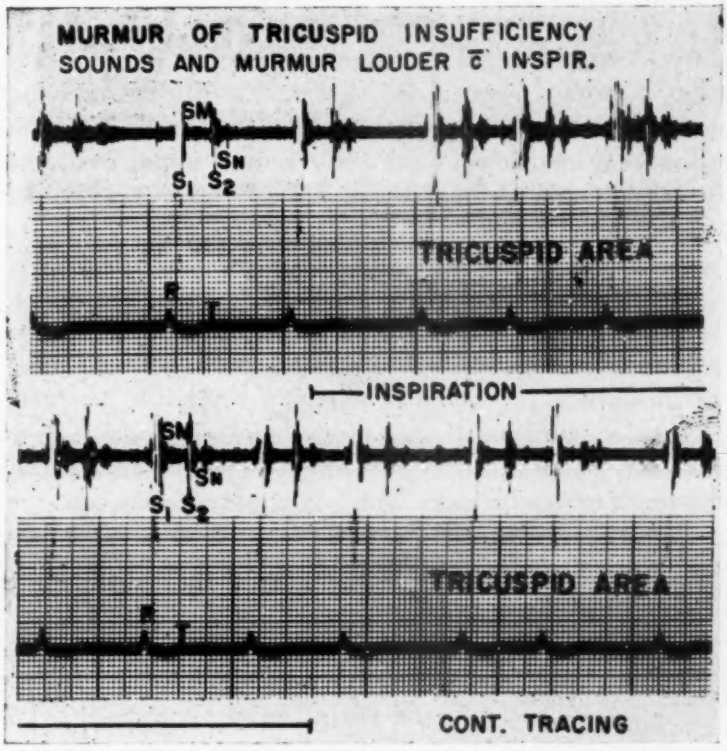
and may gradually fall off if the inspiratory phase is maintained (Fig. 6). During inspiratory apnea, an occasional patient may perform an involuntary Valsalva maneuver, which will immediately diminish the intensity of the murmur. This must be guarded against if Carvallo's sign is to be properly elicited. Not only does the murmur become louder during inspiration, but it often changes character to become high-pitched or musical (Fig. 1). We have observed that one or both heart sounds, as well as the murmur, may increase in intensity during inspiration (Figs. 1, 6, 7). This increase of sound and murmurs with inspiration



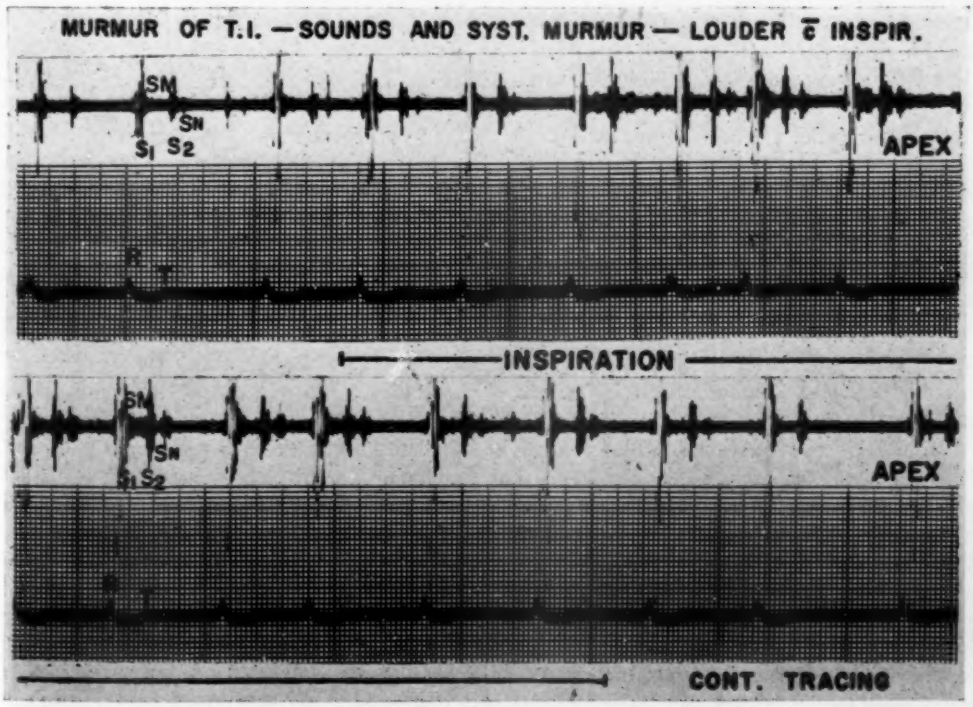
A. *B.*

Fig. 6.—36-year-old man with surgically proved mitral stenosis without insufficiency. *A*, Cardiac enlargement with prominent pulmonary artery segment. On fluoroscopy both right and left atria were enlarged. Right ventricle was markedly enlarged and mitral valve was calcified. *B*, Atrial fibrillation, early right ventricular hypertrophy and digitalis effect. *C*, Grade 3 murmur at tricuspid area became 2 grades louder with inspiration. *D*, Systolic murmur (*SM*) also heard at apex, still increased with inspiration. Note heart sounds (S_1, S_2, and *SN* the opening snap) also louder with inspiration and gradually decreased in intensity prior to expiration.

over the tricuspid and pulmonic areas can be explained by greater venous return to the right atrium during the inspiratory phase, which results in a transient increase in blood flow across the valves of the right heart.[20,21] Conversely, mitral insufficiency murmurs are not accentuated by inspiration because the right-sided hemodynamic changes are poorly transmitted to the left heart, due to the interposed pulmonary capillary bed.[21] An anatomic factor also may play a role. Mitral insufficiency murmurs tend to be transmitted to the axilla and back, and may be diminished in intensity during inspiration because expanded lung tissue is interposed between the mitral valve and the stethoscope. The more superficial and anteriorly transmitted tricuspid murmurs are not diminished by lung inflation, but rather are accentuated because of forward displacement of the heart toward the examiner's stethoscope during deep inspiration.



(Fig. 6C. For legend see opposite page.)



(Fig. 6D. For legend see opposite page.)

Not only do tricuspid sounds and murmurs become louder during inspiration, but occasionally the mitral diastolic rumbling murmur and opening snap of the mitral valve may become accentuated (Figs. 6, 7). The reason why the murmur of mitral stenosis and opening snap may become louder during inspiration, while the murmur of mitral insufficiency becomes fainter, is not clear. A number of patients have been observed who demonstrated this. Tricuspid stenosis was not thought to be present.

It is sometimes difficult to distinguish the murmur of tricuspid incompetence from that of mitral insufficiency in patients with mitral stenosis, where they may occur together.[17,20-23] In certain instances, however, it may be possible to differentiate them (Fig. 3).

Tricuspid incompetence, which is partially reversible by preoperative improvement in cardiac compensation, is not a contraindication to valvuloplasty and the patient may show much improvement following the procedure.[3,7] Tricuspid incompetence or insufficiency which fails to respond at all to preoperative care has been cited as a contraindication to surgery.[4] This has not been our experience, and some of the most gratifying results have occurred in such cases.

The following patients demonstrate the association of severe mitral stenosis and tricuspid incompetence masquerading as mitral stenosis and mitral insufficiency.

CASE REPORTS

CASE 1.—(Fig. 4.) A 57-year-old woman had had rheumatic fever at the age of 28 years. Dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea began 4 years prior to admission. Auricular fibrillation had been present 2 years, following which chronic fatigue, intermittent edema, ascites, and painful hepatomegaly gradually developed. For months there had been dull substernal aching pain, occurring with severe fatigue, lasting about 30 minutes, and relieved by rest. In spite of digitalis, salt restriction, and diuretics, disability had increased until she was bedridden.

On examination the patient was orthopneic. The blood pressure was 110/70mm.Hg. The neck veins were distended. The lungs were clear. The heart was enlarged 2 cm. beyond the midclavicular line. The rhythm was irregular. The second heart sound at the pulmonic area and the first heart sound at the apex were greatly accentuated. There were Grade 2 systolic and diastolic murmurs over the pulmonic area. At the apex, there was an opening snap and a Grade 3 diastolic rumbling murmur. A Grade 4 harsh systolic murmur, loudest just to the left of the sternum in the fifth intercostal space, was transmitted to the apex where it was Grade 3. It increased in intensity on deep inspiration. The liver was palpable 7 cm. below the right costal margin, was tender, and showed systolic pulsations. The spleen was palpated 2 cm. below the left costal margin. There was pitting edema of the ankles. The venous pressure was 230 mm. of saline.

Radiologic examination revealed a straight left heart border with a prominent pulmonary artery segment and left atrial appendage. The esophagus was displaced posteriorly by the left atrium. The right atrium and ventricle appeared to be moderately enlarged, and the left ventricle was normal. There was no systolic expansion of the left atrium or calcification of the mitral valve. An electrocardiogram showed atrial fibrillation and digitalis effect.

Prior to surgery, diuretic therapy resulted in loss of edema and concomitantly less evidence on physical examination of tricuspid incompetence. At surgery, there was tight mitral stenosis with an orifice of approximately 0.8 sq. cm. and no regurgitant jet. A satisfactory valve opening was obtained. The systolic murmur decreased a grade in intensity following surgery, but still became louder on inspiration. The patient was discharged decidedly improved. When she was seen over a year later, she had returned to work, almost completely rehabilitated.

Comment: Although there was a Grade 4 systolic murmur, it was observed to be loudest in the xiphoid region and to increase in intensity on inspiration. This, in conjunction with other evidence of tricuspid incompetence and in the absence of enlargement of the left ventricle, pointed to predominant tricuspid incompetence rather than mitral insufficiency. At surgery, tight mitral stenosis without insufficiency was found, and definite prolonged improvement followed surgery.

CASE 2.—(Fig. 5.) A 47-year-old woman had had two childhood episodes of rheumatic fever followed by mild chronic fatigue and dyspnea on exertion. During several pregnancies, severe dyspnea, orthopnea, and ankle edema occurred. The last 2 pregnancies ended in miscarriages. For several years, severe dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, and edema had been present. During the last 2 years she had cyanosis on exertion, ascites, severe edema, hepatomegaly, hepatic pain, and intermittent jaundice. Progressive incapacity developed in spite of intensive medical therapy, and she had been bedridden for months.

The patient appeared chronically ill and wasted. There was a peculiar greenish hue to her face. The sclerae were icteric and the finger tips cyanotic. The blood pressure was 120/90 mm. Hg. There was a prominent systolic pulsation in the neck veins. The chest was clear. The heart was enlarged slightly to the left of the mid-clavicular line. There was a double pulsation along the left sternal border in the second and third intercostal spaces. The cardiac rhythm was irregular. The second heart sound was accentuated over the pulmonic area, where there was a Grade 3 systolic and a Grade 2 blowing diastolic murmur. At the apex, there was an accentuated first heart sound, an opening snap, and a Grade 2 rumbling diastolic murmur. There was a Grade 4 high-pitched systolic murmur heard equally well at the apex and at the xiphoid region. This murmur increased in intensity on deep inspiration. The liver was palpated 5 fingerbreadths below the right costal margin and was tender and pulsating. The spleen was palpable 2 fingerbreadths below the left costal margin. There was a small amount of ascites and slight ankle edema. The venous pressure was 200 mm. of saline, with prominent respiratory and systolic oscillations. The icterus index was 50, and the total serum bilirubin was 3.3 mg. per 100 ml.

Radiologic examination revealed enlargement of the heart in the transverse diameter, with a straight left border and prominent pulmonary artery segment (Fig. 5). The esophagus was displaced posteriorly by the left atrium. The right atrium and ventricle were very much enlarged, and the left ventricle, slightly so. Systolic expansion of the left atrium was not observed. The mitral valve was extensively calcified. An electrocardiogram showed atrial fibrillation, frequent premature ventricular contractions, right axis deviation, and digitalis effect.

Preoperatively, there was much improvement with strict medical therapy. A diuresis occurred, jaundice disappeared, and physical evidence of tricuspid incompetence became less apparent. At surgery, the mitral valve was diffusely thickened and heavily calcified. The orifice was smaller than the tip of the index finger and less than 1.0 sq. cm. in area. A slight regurgitation jet was felt. The valve was fractured, and could be cut only with difficulty, but an opening of 2½ to 3 fingerbreadths was achieved, and there was fair motion of the cusps. Postoperatively, a dramatic clinical change occurred, with subjective and objective improvement in the congestive failure. The liver receded, and the systolic murmur at the apex and xiphoid areas decreased 2 grades in intensity, but the accentuation on deep inspiration persisted. A follow-up 1½ years later revealed persistent clinical improvement with rehabilitation.

Comment: This is a case of tight mitral stenosis and classical tricuspid incompetence with atrial fibrillation, typical murmurs, a very large right atrium and ventricle, systolic venous and hepatic pulses, ascites, jaundice, cyanosis, and edema. Often, however, tricuspid incompetence will not be so evident, and will need to be searched for by careful physical examination or cardiac catheterization. Worthy of note is the fact that tricuspid incompetence may simulate

mitral insufficiency, not only with a systolic murmur but with a large heart. In this instance, after careful fluoroscopy, the ventricular enlargement was considered to be predominantly right ventricle.

CASE 3.—(Fig. 6.) A 36-year-old man had had rheumatic fever at the ages of 11 and 21 years. Following the second episode, intermittent dyspnea, palpitation, and fatigue occurred. During the last 4 years he developed progressively severe dyspnea, orthopnea, fatigue, palpitation, hemoptysis, and hepatomegaly. Venous pulses in the neck and profuse perspiration had been noted recently. Treatment with digitalis, salt restriction, and diuretics resulted in only transient improvement. He was unable to work or to perform any physical activity without discomfort.

The patient was dyspneic at rest. The blood pressure was 120/70 mm. Hg. The neck veins were distended and pulsating. Inspiratory râles were present at the right lung base. There was a prominent pulsation over the xiphoid region and left sternal border. At the apex, there was an accentuated first heart sound, an opening snap, and a Grade 3 rumbling diastolic murmur. A systolic murmur at the xiphoid area increased from Grade 3 to 4 on deep inspiration. It was transmitted slightly to the apex but still became louder with inspiration. A very firm liver was palpable 5 fingerbreadths below the right costal margin and pulsated slightly. The spleen was palpable 2 fingerbreadths below the left costal margin. The venous pressure was 240 mm. of saline.

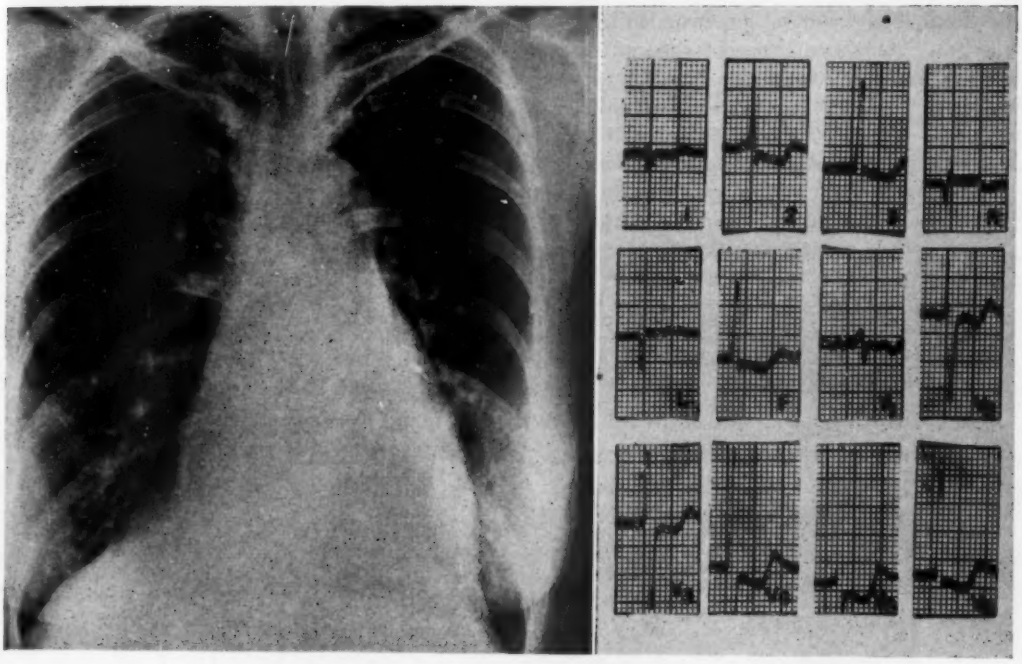
Radiologic examination revealed enlargement of the heart in the transverse diameter, with a straight left border. The pulmonary artery, left atrium, and right atrium were definitely enlarged. Both ventricles appeared to be enlarged, the right ventricle markedly so. There was extensive calcification of the mitral valve. Systolic expansion of the left atrium was not observed. There was severe pulmonary congestion. An electrocardiogram showed atrial fibrillation and early right ventricular hypertrophy.

Preoperatively, medical therapy did not result in an improvement in compensation. At surgery, a very thick, deformed, calcified mitral valve with severe stenosis was present. The total valve area was estimated between 0.5 and 1.0 sq. cm. There was no regurgitant jet. A good valve opening with fair motion of the cusps was obtained. Postoperatively, there was less dyspnea. The liver receded 2 fingerbreadths, and a diuresis occurred. The murmur of tricuspid incompetence persisted. This patient was operated on very recently and it is expected that further improvement will occur.

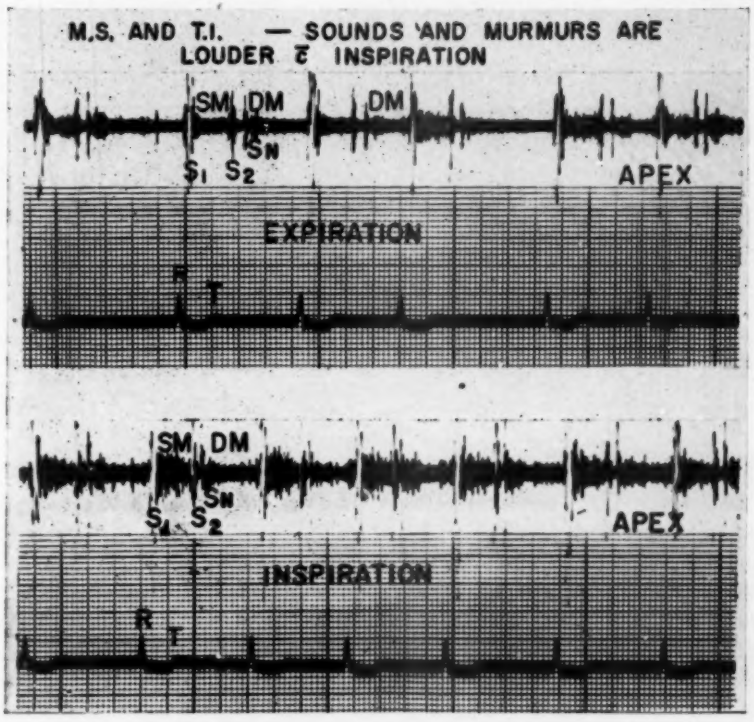
Comment: The patient had mitral stenosis with tricuspid incompetence and severe congestive failure, and it was impossible to promote a diuresis or to improve compensation to any degree with medical therapy. He tolerated surgery well, and clinical improvement occurred immediately following it. This has been observed in other patients. In our experience, tricuspid incompetence which fails to respond to medical therapy is not a contraindication to mitral surgery.

CASE 4.—(Fig. 7.) A 47-year-old woman had growing pains and frequent nosebleeds during childhood. For several years she had noticed increasing dyspnea on exertion, orthopnea, ankle edema, a chronic cough, irregular palpitation, and chronic fatigue. Digitalis, salt restriction, and diuretics had resulted in only slight improvement. The patient was unable to walk short distances without dyspnea, but was comfortable at rest.

The lungs were clear. The blood pressure was 140/76 mm. Hg. The neck veins were slightly distended. The heart was slightly enlarged and the rhythm grossly irregular. The pulmonic second sound was louder than the aortic second sound. A Grade 2 systolic murmur and a Grade 3 diastolic murmur were present over the pulmonic area. At the apex, the first heart sound was much accentuated, and there was an opening snap followed by a Grade 3 rumbling diastolic murmur. There was a systolic murmur heard equally well in the tricuspid and mitral areas that increased in intensity from Grade 2 to Grade 3 on deep inspiration. It was poorly transmitted laterally. The liver was barely palpable.



A. *B.*



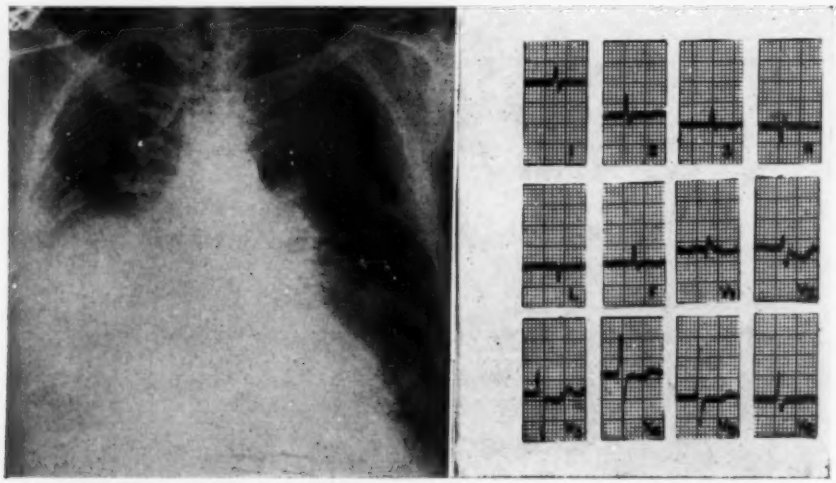
C.

Fig. 7.—47-year-old woman with surgically proved pure tight mitral stenosis. *A*, Pulmonary emphysema and cardiac enlargement. Dilated aorta. On fluoroscopy pulmonary artery, both atria, and right ventricle were enlarged. Mitral valve was calcified. *B*, Atrial fibrillation, early right ventricular hypertrophy and digitalis effect. *C*, Systolic murmur (*SM*) Grade 2 increased to Grade 3 on inspiration. (Murmur heard well at apex and tricuspid area, poorly transmitted laterally.) Note increase in heart sounds (S_1, S_2). Opening snap (*SN*) and diastolic rumble (*DM*) also increase with inspiration.

Radiologic examination revealed pulmonary fibrosis and emphysema, with bleb formation. The heart was moderately enlarged in the transverse diameter, with a straight left border. The aorta was dilated and tortuous. The pulmonary artery, both atria, and the right ventricle were enlarged. There was questionable enlargement of the left ventricle. The mitral valve was calcified. Systolic expansion of the left atrium was not seen. An electrocardiogram showed atrial fibrillation and early right ventricular hypertrophy.

Preoperatively, a weight loss of 5 pounds occurred with diuretic therapy. At surgery, a very tight mitral stenosis, with an opening of about 0.5 sq. cm., was fractured with ease. Postoperatively, there was dramatic clinical improvement.

Comment: The systolic murmur was heard well at the xiphoid area and apex, but became louder during inspiration. Although there was no other physical evidence of tricuspid incompetence, it was thought that this murmur resulted from mild tricuspid incompetence and did not represent mitral insufficiency. At surgery, no mitral insufficiency was found.



A. *B.*

Fig. 8.—51-year-old man with tight mitral stenosis with mitral insufficiency at surgery. He had evidence of tricuspid incompetence clinically and at catheterization. *A*, Cardiac enlargement—predominantly right atrium and ventricle. *B*, Atrial fibrillation and early right ventricular hypertrophy. *C*, Systolic murmur Grade 2 at apex (upper tracing); Grade 4 in tricuspid area (lower tracing).

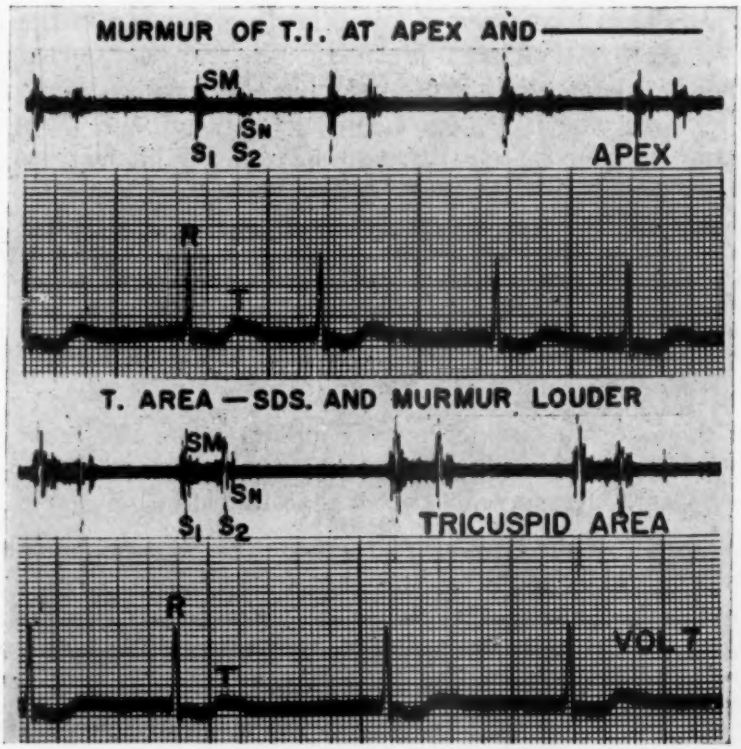
CASE 5.—(Fig. 8.) A 51-year-old man had had rheumatic fever at the age of 14 years. A murmur had been noted at the age of 21 years. Since 35 years of age, he had taken digitalis for an irregular heart. For several years dyspnea on exertion, orthopnea, intermittent edema, and paroxysmal nocturnal dyspnea had become progressively more severe. Recently, he had developed anasarca and a pleural effusion in spite of intensive medical therapy.

The patient was thin and orthopneic. There was neck vein distention with systolic expansion. There was a right pleural effusion. The heart was enlarged. The second pulmonic sound was accentuated. At the apex, an opening snap and a Grade 3 mid-diastolic rumbling murmur were present. A Grade 4 high-pitched systolic murmur in the xiphoid area radiated toward the apex where it was Grade 2. A slight increase in the intensity of the murmur during inspiration was observed during the early hospital course, but this disappeared with improvement in compensation. The liver was enlarged 3 fingerbreadths below the right costal margin and pulsated slightly. The spleen was palpated 2 fingerbreadths below the left costal margin and there was 3 plus edema of the legs.

Radiologic examination revealed the heart to be greatly enlarged in the transverse diameter. The pulmonary artery and left atrium were moderately enlarged, and the right atrium, markedly so. Both ventricles were enlarged, particularly the right. Valve calcification and systolic expansion of the left atrium were not seen. There was a large right pleural effusion and severe pulmonary congestion. The electrocardiogram showed atrial fibrillation and early right ventricular hypertrophy. Cardiac catheterization revealed pulmonary hypertension with a pressure of 72/35 mm. Hg, a right atrial pressure curve contour of tricuspid incompetence, and an arterial oxygen saturation of 92 per cent. The cardiac output was 4.4 L. per minute at rest.

Preoperatively, thoracentesis and diuretic therapy resulted in a weight loss of 20 pounds, with improvement in symptoms. The murmur of tricuspid insufficiency persisted, but no longer increased with inspiration. At surgery, there was a tight mitral stenosis of less than 1 sq. cm. area, with an atrioventricular end-diastolic filling gradient of 26 mm. Hg. A satisfactory valvuloplasty was accomplished, with an immediate fall in the gradient to about 4 mm. Hg. He was operated upon only recently and is improving steadily.

Comment: The tricuspid insufficiency in this patient was accompanied by a systolic murmur that was much louder in the xiphoid and left parasternal area than it was at the apex. During inspiration it became only slightly louder. In such instances the location of maximum intensity of the murmur may prove more helpful than Carvallo's sign in suspecting tricuspid incompetence.



(Fig. 8C. For legend see opposite page.)

DISCUSSION

These patients are representative of an important group with mitral stenosis that is frequently denied the benefit of surgery because of the erroneous diagnosis

of associated mitral insufficiency. All proved to have tight mitral stenosis at surgery,* without significant insufficiency. They were suspected initially of having significant mitral insufficiency because of a loud apical systolic murmur. On careful evaluation the systolic murmur proved to be that of tricuspid incompetence. In addition to the murmur of tricuspid incompetence, the following features were usually present: atrial fibrillation, other physical evidence of tricuspid incompetence, and severe right heart failure. Functional pulmonary systolic murmurs were common, and the functional murmur of pulmonary insufficiency (Graham Steell murmur) was usually loud, probably resulting from a more severe degree of pulmonary hypertension. An occasional patient had only the systolic murmur as evidence of tricuspid incompetence, and in the less severe case it sometimes disappeared on medical therapy.

A uniformly good result followed surgery and was accompanied by less physical evidence of tricuspid insufficiency. The murmur invariably became fainter, but usually persisted to some degree.

In the selection of patients for surgical treatment of mitral stenosis, it is apparent that one should search carefully for tricuspid insufficiency with a murmur masquerading as mitral insufficiency. Utilizing this observation, the following clinical criteria have been of value in diagnosis and in the elimination of significant degrees of associated mitral insufficiency: (1) evidence of a large dynamic left ventricle on physical examination, electrocardiogram, or radiologic examination, (2) an unusually large (giant) left atrium, and (3) a loud apical systolic murmur that decreased rather than increased in intensity on inspiration.

SUMMARY

1. Five cases of severe mitral stenosis with associated tricuspid incompetence that masqueraded as mitral insufficiency are presented.

2. They were suspected of having significant mitral insufficiency chiefly because of a loud systolic murmur in the apical area.

3. The systolic murmur which was loudest along the lower left sternal border and xiphoid region, and which increased in intensity on deep inspiration, was due to tricuspid incompetence rather than mitral insufficiency.

4. In addition to the tricuspid murmur, other features commonly present were: atrial fibrillation, advanced right heart failure, loud functional pulmonic murmurs, and other physical evidence of tricuspid incompetence. Cardiomegaly was greater than usual in mitral stenosis because of more advanced right ventricular hypertrophy.

5. At surgery, severe mitral stenosis without insufficiency was discovered, and operation was followed by uniformly good results.

6. They represent a group of incapacitated patients that often are denied surgery for mitral stenosis when they could be benefited.

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*Operations performed by Dr. Charles A. Hufnagel, Associate Professor of Surgery, Georgetown University Medical Center.

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CHEST DEFORMITY IN CHILDREN WITH CONGENITAL HEART DISEASE

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INTRODUCTION

DEFORMITY of the chest is a common finding in pediatric practice. This is especially so in children with congenital heart disease. It is the purpose of this paper to consider the genesis of the phenomenon in this group, and to offer some comments upon deformity of the chest in general.

PRELIMINARY OBSERVATIONS

It has been suggested that chest-bulging may occur in such conditions as tetralogy of Fallot. This was ascribed to right ventricular hypertrophy by Taussig,[1] and others. It is perhaps significant that total cardiac enlargement is not a constant association in this disease.[2] Similar chest deformities have been described in left-to-right shunts.[3,4]

In considering the cause of this deformity, other conditions will first be reviewed. Thus, Brenneman[5] notes that unilateral chest-bulging may be found in infants with the common "head-flattening" of infancy; he points out that the "bulge" is in reality the normal side of the chest, which contrasts with the flattened side. This syndrome, if it may be called such, is found in torpid, inactive infants. Certain children with congenital heart disease, especially of the cyanotic variety, are notoriously so. Thus, the author occasionally has discovered such "bulges" in his series of congenital cardiac defects, but on follow-up was surprised to observe their disappearance. The coincidence with head-flattening, which disappears with the chest deformity on walking, explained this observation. Asymmetry of the chest, giving rise to an apparent unilateral bulge, is not uncommonly associated with a mobile scoliosis.[6] The latter is more common in hypotonic children; children with severe congenital heart disease are sometimes hypotonic. Thus, these sources of observer error should be considered in the frequency with which chest deformity is attributed to congenital heart disease. However, it has been the author's experience that chest deformity is common in congenital heart disease even when the above-mentioned sources of error are excluded. Table I, composed from consecutive cases seen in 1954-55 illustrates this point.

Therefore, the association of these deformities with congenital cardiac defects is not in doubt, but the hypothesis that they are due to cardiomegaly alone is unsatisfactory. A review of Mannheimer's protocols of tetralogy of Fallot[7] (e.g., Case 11) suggested that a "bulge" of the chest was found although only minimal cardiac enlargement was present. Undoubted cases of cardiomegaly in large left-to-right shunts with chest deformity have been described by Barber,[4] and others. It has been shown by the present author that a common denominator

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in many types of congenital heart disease is frequent respiratory infection.[8] Table II illustrates this point, showing that the direction of shunt is not material, and giving evidence of the frequency of the respiratory complication. It has been the author's experience that chest-bulging or other deformity is not found in "pure" pulmonary stenosis, nor in coarctation of the adult type. In these conditions, right and left ventricular hypertrophy are common, but respiratory infections of all types are not abnormally increased in incidence.

TABLE I. INCIDENCE OF CHEST DEFORMITY IN CONGENITAL HEART DISEASE

LESION	TOTAL	NUMBER AFFECTED	PER CENT
Tricuspid Atresia	3	3	100*
Tetralogy of Fallot	40	16	40
Transposition	13	6	46
Atrial Septal Defect	41	21	51
Ventricular Septal Defect	18	9	50
Patent Ductus Arteriosus	27	6	22

*Of those surviving 6 months or more.

TABLE II.* INCIDENCE OF RESPIRATORY INFECTIONS IN CLINICAL HISTORY

DISEASE	TOTAL	RESPIRATORY INFECTION	PER CENT
Tetralogy of Fallot	33†	18	54
Transposition of Great Vessels	13†	8	61
Tricuspid Atresia	6†	2	33
Pure Pulmonary Stenosis	8	0	0
Pulmonary Stenosis R-to-L Shunt—Normal Aortic Root	5	2	40
Coarctation, Adult Type	10	0	0
Coarctation with L-to-R Shunt (A.S.D., V.S.D., P.D.A.)	8	5	63
Atrial Septal Defect	41	27	69
Ventricular Septal Defect	22	13	59
Patent Ductus Arteriosus	27	18	66

*Reproduced from American Heart Journal 53:830, 1957.
†Surviving 3 months or more.

The most common deformity is a bilateral diaphragmatic sulcus, first described by Edwin Harrison, in 1837.[9] The grooves were considered to be a sign of rickets, and to be caused by diaphragmatic contraction. Naish and Wallis[10] considered the condition to be due to "deficient lung expansion" and associated it with asthma. Naish[11] noted the presence of the sulci in congenital heart disease, as had Sheldon,[12] who thought they were due to atelectasis. "Bulging" above the sulci is not uncommon, but may not be real. The normal "round" thorax of the infant should be kept in mind when assessing the chest in the younger age group.

This shape of thorax, when viewed above the diaphragmatic grooves, may give a spurious impression of chest-bulging.

Naish and Wallis[10] observed Harrison's sulci in 45 per cent of children over the age of 5 years. They were considered "obvious" if greater than $^3/_{16}$ inch.

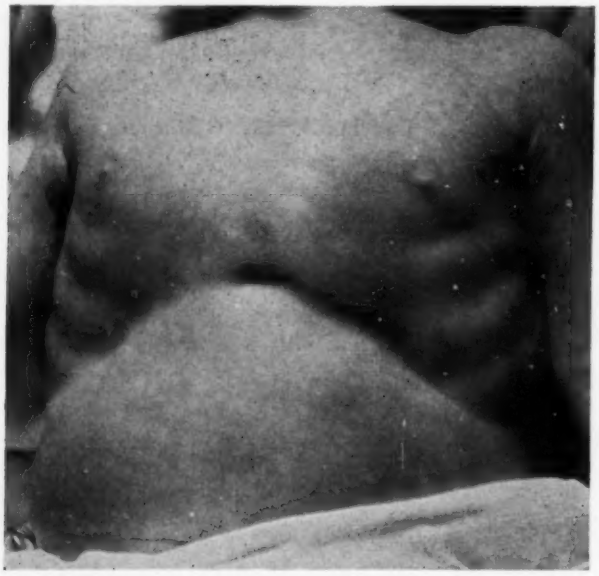

Fig. 1.—Infant with bronchiolitis. Note lower rib-retraction and apparent "apical" bulging.

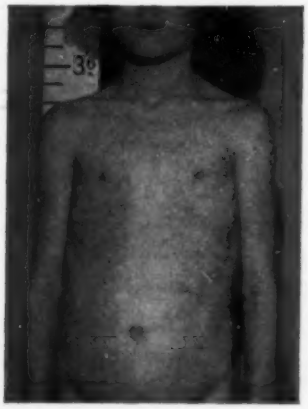

Fig. 2.—Eight-year-old child with fibrocystic disease of pancreas, Harrison's sulci, and early pigeon-breast deformity. Heart size normal.

This author has found that obvious sulci by this criterion are hardly ever found in "normal" children before the age of 3 years. They are never found in the first year except in the presence of respiratory infection or obstruction. "Acute" Harrison's sulci may occur in the presence of severe respiratory obstruction. Apparent "apical" bulging may be seen in such conditions as infantile bronchiolitis. Fig. 1 illustrates a typical case; this deformity is usually reversible after

the acute episode is over. A similar picture is seen in asthmatics; this is more likely to become permanent because of frequent attacks of bronchospasm. The chest deformity of pancreatic fibrosis is illustrated in Fig. 2; this patient had no cardiomegaly. A similar lesion is seen in Figs. 3 and 4, patients with tetralogy of Fallot and left-to-right shunt, respectively. The feature common to these 3 patients was frequent respiratory infections. Fig. 5 shows the sulcus and apparent

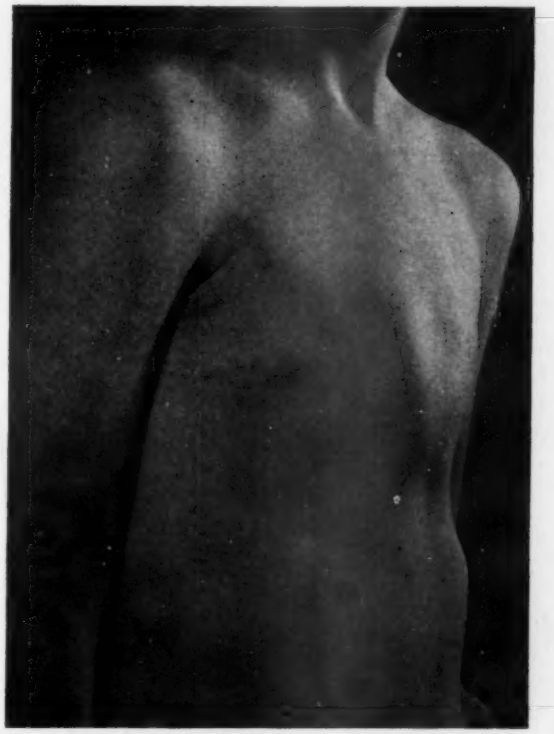

Fig. 3.—Tetralogy in a child aged 9 years. Bilateral Harrison's sulci and sternal depression giving rise to spurious upper chest "bulge." Heart not enlarged; frequent respiratory infections.

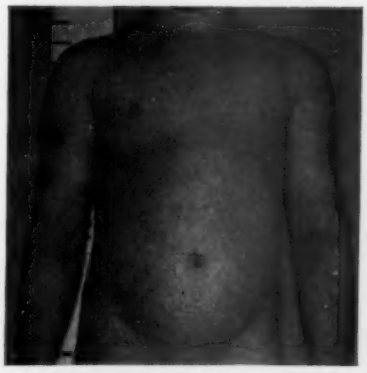

Fig. 4.—Atrial septal defect with enlarged heart and frequent respiratory infections. Note deep Harrison's sulci.

This shape of thorax, when viewed above the diaphragmatic grooves, may give a spurious impression of chest-bulging.

Naish and Wallis[10] observed Harrison's sulci in 45 per cent of children over the age of 5 years. They were considered "obvious" if greater than $^3/_{16}$ inch.

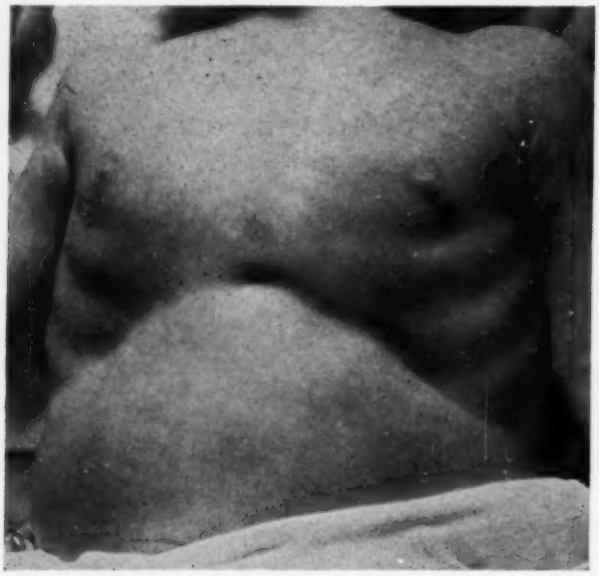

Fig. 1.—Infant with bronchiolitis. Note lower rib-retraction and apparent "apical" bulging.

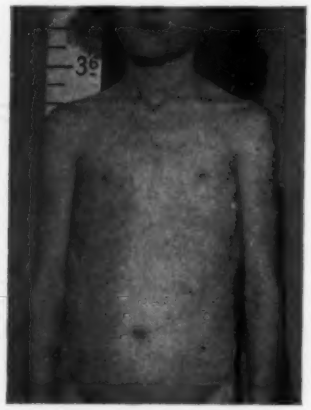

Fig. 2.—Eight-year-old child with fibrocystic disease of pancreas, Harrison's sulci, and early pigeon-breast deformity. Heart size normal.

This author has found that obvious sulci by this criterion are hardly ever found in "normal" children before the age of 3 years. They are never found in the first year except in the presence of respiratory infection or obstruction. "Acute" Harrison's sulci may occur in the presence of severe respiratory obstruction. Apparent "apical" bulging may be seen in such conditions as infantile bronchiolitis. Fig. 1 illustrates a typical case; this deformity is usually reversible after

the acute episode is over. A similar picture is seen in asthmatics; this is more likely to become permanent because of frequent attacks of bronchospasm. The chest deformity of pancreatic fibrosis is illustrated in Fig. 2; this patient had no cardiomegaly. A similar lesion is seen in Figs. 3 and 4, patients with tetralogy of Fallot and left-to-right shunt, respectively. The feature common to these 3 patients was frequent respiratory infections. Fig. 5 shows the sulcus and apparent

Fig. 3.—Tetralogy in a child aged 9 years. Bilateral Harrison's sulci and sternal depression giving rise to spurious upper chest "bulge." Heart not enlarged; frequent respiratory infections.

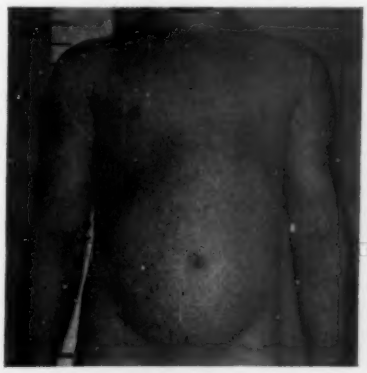

Fig. 4.—Atrial septal defect with enlarged heart and frequent respiratory infections. Note deep Harrison's sulci.

bulge on the chest x-ray; the position of the heart in relation to this is worthy of note. Geographically, there is no relationship, and no true chest-bulge was seen. This patient had a moderately enlarged heart due to a ventricular septal defect, but, in addition, had suffered frequently from bronchitis since early in life.

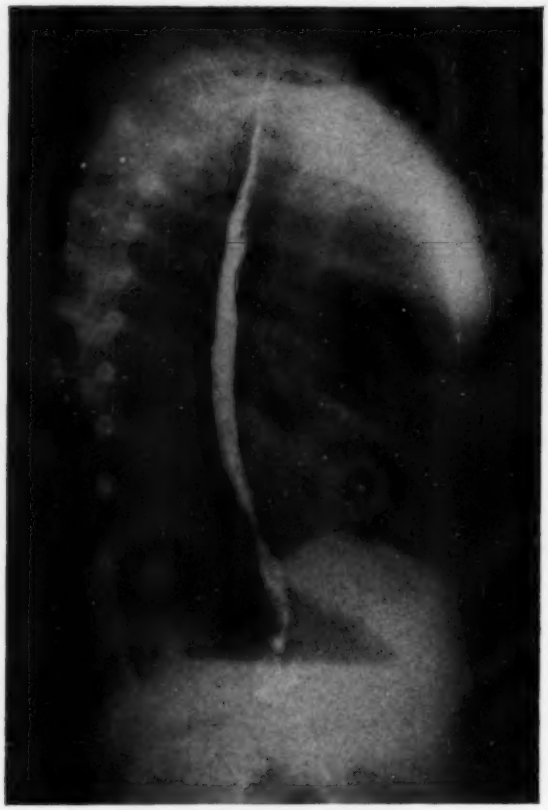

Fig. 5.—Left-to-right shunt with Harrison's sulci. Note lack of relationship of heart to the apparent "bulge" in the upper chest.

PIGEON-BREAST

Bilateral Harrison's grooves and chest-bulging may, with sternal deformity, progress to the so-called "pigeon-breast." This association was seen by Naish and Wallis,[10] who felt that it was almost always due to rickets. The "pigeon-breast" has been seen by the author in his series of patients with congenital heart disease. Fig. 6 illustrates the deformity in a 20-year-old boy with a patent ductus, gross cardiomegaly, and frequent respiratory infections. No evidence of healed rickets was present on x-ray. Fig. 7 illustrates the condition in a child with transposition; there was neither radiologic nor biochemical evidence of rickets. His vitamin D intake had been supervised personally and was adequate. He had frequent respiratory infections. Fig. 8 shows the same lesion in a patient with bronchiectasis, and pulmonary failure with a high functional residual capacity. Radiologically, the heart size was "normal" in all views. Again there

was no clinical or radiologic evidence of rickets, and vitamin D intake had been, if anything, more than adequate.

The common factor, therefore, in some cases of "pigeon-breast" is respiratory infections. This is true of Harrison's sulci also, and agrees with Naish and Wallis' opinion[10] that rickets does not cause these grooves. In addition, there is evidence that "pigeon-breast" is not a rachitic deformity and that it is commonly associated with respiratory infections; these latter troubles are, of course, common enough in true rickets.[18]

Fig. 6.—Bilateral Harrison's sulci and "pigeon-breast"; patent ductus with frequent respiratory infections.

The natural history of the chest deformity in congenital heart disease is of interest. As already intimated, the Harrison's sulci are the first to appear, and are associated with respiratory infections, or less commonly, with gross dyspnea at rest. While "mobile" in the first attacks of respiratory infection, the grooves become fixed by the first birthday. They are emphasized perhaps by the general malnourishment so common in the affected group, and the chest appears to "bulge" above the grooves. However, the chest circumference at the nipple line remains small, reflecting the general small size of the patient, and head-chest circumference ratio is not lost. If the bulging were true, it seems likely that these measurements would be disturbed.

The condition may, with the appearance of sternal protrusion, progress to the so-called "pigeon-breast"; this is variable in onset, but may occur by the age of 18 months (see Fig. 7). It remains a fixed deformity thereafter, and does not regress even if the number of respiratory infections is reduced by successful opera-

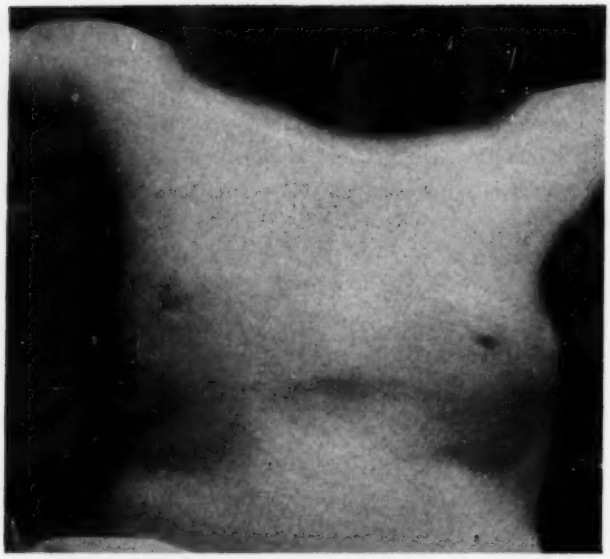

Fig. 7.—Transposition in infant aged 18 months. Note Harrison's sulci and early sternal protrusion cardiomegaly and frequent respiratory infections.

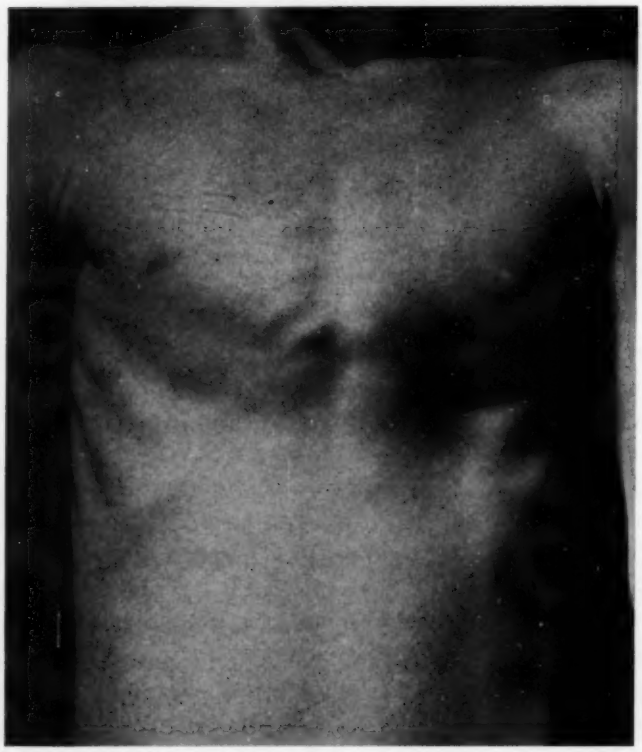

Fig. 8.—Chest deformity in a case of bronchiectasis.

tion appropriate to the lesion. It is, however, less obvious because of the improvement in nutrition subsequent to surgical cure. The condition is not preventable by vitamin prophylaxis.

SUMMARY AND CONCLUSIONS

Some sources of error in the assessment of chest deformity in congenital heart disease are mentioned. The early deformity is Harrison's grooves, which would not appear to be rachitic. These may give rise to apparent chest-bulging. The condition may progress to the "pigeon-breast" deformity. The chest changes occur in a variety of congenital cardiac defects, the presence of cardiomegaly and the direction of shunt being immaterial. The common factor is respiratory disease or, less often, dyspnea. Rickets may be excluded as a primary cause of both Harrison's sulci and of "pigeon-breast" in cardiac patients.

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THE EFFECT OF A SINGLE INTRAVENOUS DOSE OF SCILLAREN† B ON THE PULMONARY CIRCULATION AND RENAL FUNCTION IN PATIENTS WITH RHEUMATIC HEART DISEASE

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THE glycosides of squill are the oldest heart-acting drugs known. The diuretic effect in certain states of dropsy and the slowing effect on the heart rate were both described before Withering published his observations on digitalis. The diuretic action had been noted several centuries earlier, e.g., by Pythagoras (570-500 B.C.).[6] Squill, however, was never used extensively because of the uncertainty of the action of the crude drug and its many side effects on the gastrointestinal tract. The purification of the glycosides Scillaren A and B by Stoll[9] gave preparations of uniform potency that have been used in clinical practice as an alternative to the digitalis glycosides. There is general agreement that Scillaren has a digitalis-like action which is rapidly established after its administration. Some authors claim that it also has a marked diuretic action, but this is not uniformly accepted.[7,8]

After the demonstration that lanatoside C had a direct renal effect in some patients with mitral valvular disease,[4] it was thought to be of interest to study the action of Scillaren, using the same experimental method, in view of the reported renal effect of this drug.

MATERIAL

Six patients with rheumatic valvular disease were studied. All had mitral stenosis, one with marked mitral incompetence, one with aortic incompetence, and two with complicating tricuspid lesions (one stenosis and one incompetence). None received any digitalis on the days prior to the study. Two of the cases with pure mitral stenosis had been studied 4 years earlier, when the acute effect of lanatoside C was investigated. They had been on digitalis for irregular periods between the studies. Heart size and other relevant clinical data appear in Table I.

METHODS

All patients were studied in the morning, recumbent, and in the postabsorptive state. An indwelling catheter was placed in the urinary bladder. An intravenous infusion of para-aminohippurate and inulin was given with the aid of a constant injection syringe after a priming dose

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†The Scillaren used in the present study was placed at our disposal by the Sandoz Company.

TABLE I. CLINICAL DATA

CASE NUMBER	SEX	AGE (YEARS)	BSA M.²	HEART VOLUME ML./M.² BSA	GROUP	HISTORY OF RHEUMATIC INFECTION	DURATION OF SYMPTOMS (YEARS)	SYMPTOMS				MURMURS			RHYTHM	DAYS BEFORE STUDY DIGITALIS MEDICATION WAS DISCONTINUED	SCILLAREN (MG.)	DIAGNOSIS
								ORTHOPNEA	HEMOPTYSIS	PULMONARY EDEMA	APICAL SYSTOLIC	APICAL MID-DIASTOLIC	APICAL PRESYSTOLIC				
1044	F	37	1.61	810	II-III	26	10	−	−	−	+	+	−		AF	1	0.5	AS, AI, MS
1046	F	48	1.84	470	III	40	7	+	−	−	+	+	−		AF	7	1.0	AI, MS, TI
1047	M	44	1.90	580	II	0	29	+	−	−	+	+	−		AF	21	1.0	MS, MI
1049	F	50	1.60	670	III	0	14	+	+	−	+	+	−		AF	3	1.0	MS
1050	F	42	1.58	500	II-III	26	8	+	−	−	+	+	−		AF	2	0.5	MS
1051	F	43	1.72	520	II	0	6	−	−	−	+	+	+		SR	10	0.5	MS, TS

AF = auricular fibrillation; SR = sinus rhythm; AS = aortic stenosis; AI = aortic incompetence; MS = mitral stenosis; MI = mitral incompetence; TI = tricuspid incompetence; TS = tricuspid stenosis; BSA = body surface area.

TABLE II. BLOOD PRESSURES, CARDIAC OUTPUT AND RENAL DATA IN 6 PATIENTS WITH RHEUMATIC HEART DISEASE BEFORE AND AFTER INTRAVENOUS ADMINISTRATION OF SCILLAREN B

CASE NUMBER	TIME	PULSE RATE BEAT/MIN.	O_2 CONSUMPTION ML./MIN.	A-V O_2 DIFFERENCE ML./L.	CARDIAC INDEX L./MIN./M.^{2} BSA	STROKE INDEX ML./BEAT/M.^{2} BSA	BLOOD PRESSURES (MM. Hg)										CLEARANCE/1.73 M.^{2} BSA		
							PCV	RA	PA			BA			RV		INULIN ML./MIN.	PAH ML./MIN.	$\mu Eq./MIN.$ Na^+
							M	M	S	D	M	S	D	M	S	D			
1044	B^{I}	87	232	38	3.76	43	13	1											
	B^{II}	79	221	39	3.53	45			25	12	18	170	77	110			103	376	610
	7.5′	80	223	42	3.31	41			21	9	14	162	74	104			111	387	652
	28′	81	217	40	3.36	41		−1	—	—	—	156	67	99	22	0	109	389	549
																	98	335	506
																	101	362	551
1046	B^{I}	88	223	53	2.30	26		7	64	34	43	189	95	128					
	B^{II}	90	254	53	2.60	29			64	34	44	187	95	128			58	245	247
	10.5′	71	255	52	2.69	38			63	28	39	188	88	125			61	252	222
	29.5′	59	241	49	2.66	45			49	23	31	173	72	105			57	229	195
	60.5′	59	222	47	2.59	44		4	53	23	31	177	65	101	55	5	66	252	211
				BA-RA															
1047	B^{I}	108	221	64	1.81	17		1											
	B^{II}	108	231	65	1.87	17			—	—	—	188	119	142			83	293	489
	11′	65	251	60	2.19	34	20′7	−1	—	—	—	173	106	128			93	319	1072
	32.5′	69	241	56	2.28	33		0	—	—	—	173	109	128			85	278	838
	48′	79						−1	—	—	—	161	102	121			102	286	720
	58′	64	224	61	1.92	30		−1				156	102	116			90	270	460
	69′	70						−1									87	260	355

1049	B^{I}	86	186	70	1.66	19		2	87	48	65	173	107	132					
	B^{II}	90	193	75	1.62	18			87	48	65	173	112	139			97	242	443
	10′	76							74	43	52						73	211	318
	19.5′	62	188	73	1.62	26			59	27	43	164	91	106			86	199	281
				BA-RA															
	37.5′	50	178	81	1.38	28		1	—	—	—	156	86	103			85	234	334
1050	B^{I}	113	160	72*	1.42	13	15	3	31	19	25	—	—	—					
	B^{II}	106	170	70	1.53	14			29	18	25	—	—	—			66	243	187
	11.5′	95	161	64	1.59	17			25	13	19	—	—	—			73	261	283
	28′	67	164	63	1.64	24			23	14	19	—	—	—			65	235	156
	43′	70	—	—	—	—		1	21	12	17	—	—	—			65	170	180
1051	B^{I}	73	192	64	1.73	24	9	8											
	B^{II}	73	176	70	1.47	20			21	11	13	119	63	86			69	244	44
	11.5′	68	210	63	1.94	29			19	10	14	145	65	97			68	211	43
	30.5′	63	196	62	1.85	29			18	8	11	160	81	108			88	273	60
				BA-RA															
	54′	65	184	57	1.88	29		5									74	259	66
																	67	248	63

*BA = 93 per cent of capacity.

BSA = body surface area; PCV = pulmonary capillary venous; RA = right atrium; PA = pulmonary artery; BA = brachial artery; RV = right ventricle; PAH = para-aminohippurate.

The pulmonary artery was catheterized according to the technique of Cournand and Ranges, and an indwelling arterial needle was placed in either brachial artery. Subsequently, the bladder was emptied and the first urine collection period started. Every 15 to 17 minutes the bladder was again emptied and rinsed twice with distilled water and air. Simultaneously a blood sample for clearance determination was taken from the brachial artery.

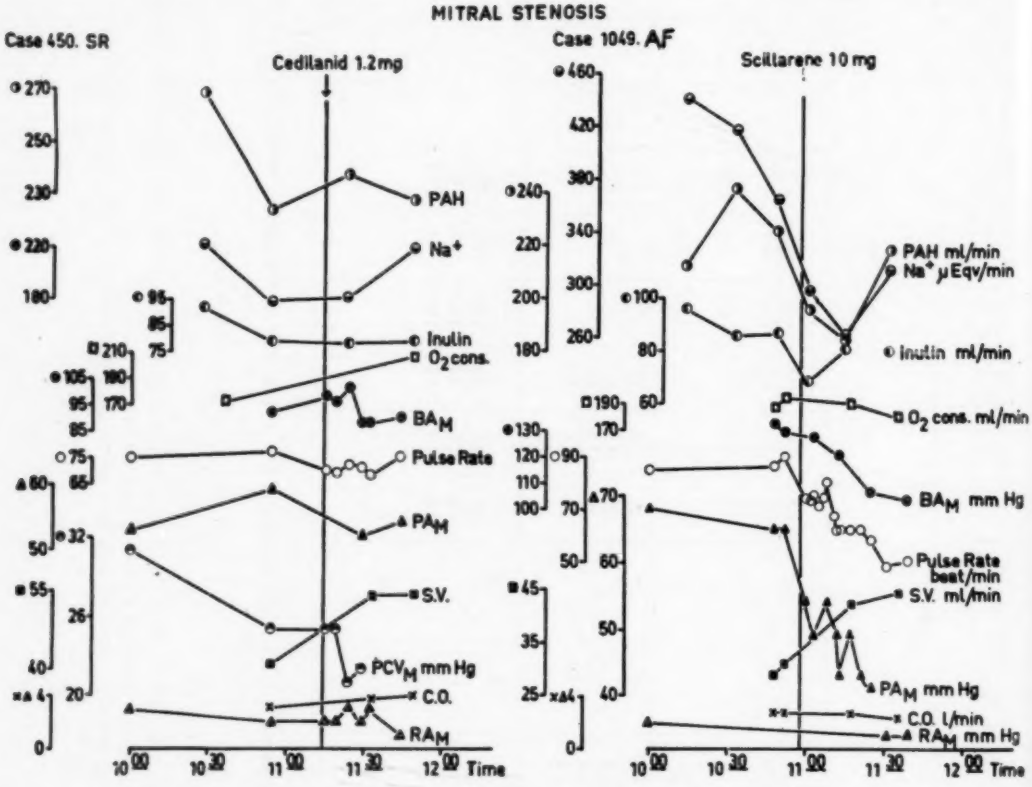


Fig. 1.—A comparison between the effect of a single intravenous dose of Cedilanid and Scillaren in the same patient, 4 years apart. During this time the patient developed auricular fibrillation and a progress of clinical symptoms. Na^+ = sodium, S.V. = stroke volume, C.O. = cardiac output. For other abbreviations see Tables I and II.

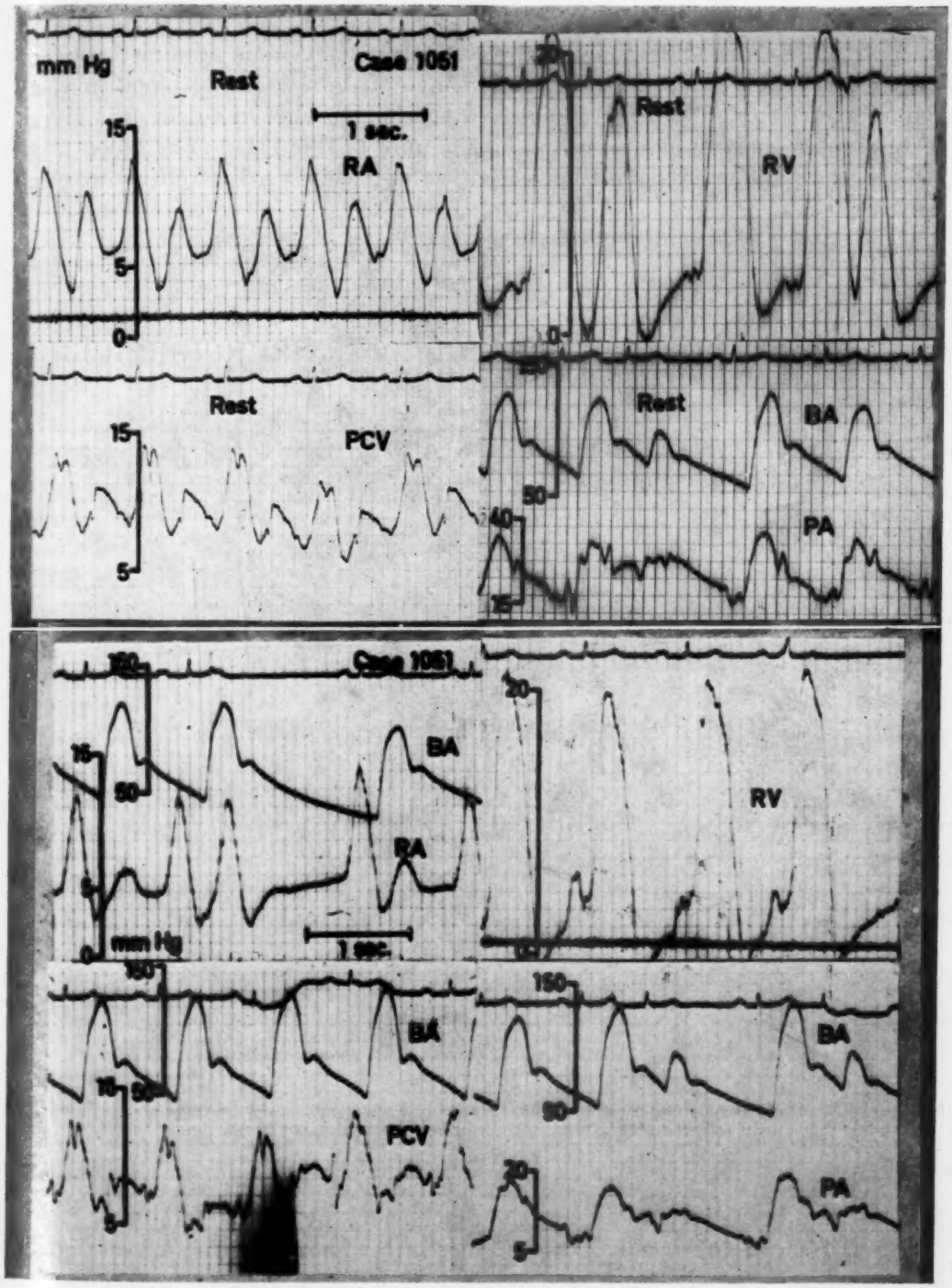
About 30 minutes after the tip of the heart catheter had been placed in the pulmonary artery, the first resting cardiac output was determined by the Fick method, with simultaneous sampling of blood from the brachial and pulmonary arteries and collection of expired air. Immediately afterwards pulmonary arterial and pulmonary capillary venous pressure were registered with the Elema strain gauge manometer. In some cases the right auricular pressure was registered simultaneously through a second catheter; in the remaining cases the right auricular pressure was registered when the catheter was introduced.

When the pressures had been registered, the bladder was rapidly emptied.

Immediately afterwards, and under continuous registration of the brachial arterial pressures and electrocardiogram, Scillaren B was given in the pulmonary artery in a dose varying between 0.5 and 1.0 mg. The injection was completed in 1 to 2 minutes.

During the following hour all observations were repeated several times. The first urine collection period was completed within 6 minutes after the drug was given. The following collection periods were all about 15 minutes in duration. The blood pressures were measured repeatedly, the cardiac output twice again, 10-12 and at about 30 minutes after the drug had been given.

A.



B.

Fig. 2.—Blood pressures in a case of tricuspid and mitral stenosis, before (*A*) and 40 minutes after (*B*) 0.5 mg. Scillaren B.

RESULTS

Table II lists the blood pressures, cardiac output, and the renal data in the patients, before and immediately after the intravenous administration of Scillaren B. There was no significant change of diuresis, renal blood flow, or sodium excretion. The heart rate decreased rapidly when the drug was given, in some cases as early as during the first minute (Table III). The blood pressures in the pulmonary circuit decreased swiftly, while cardiac output was unaltered.

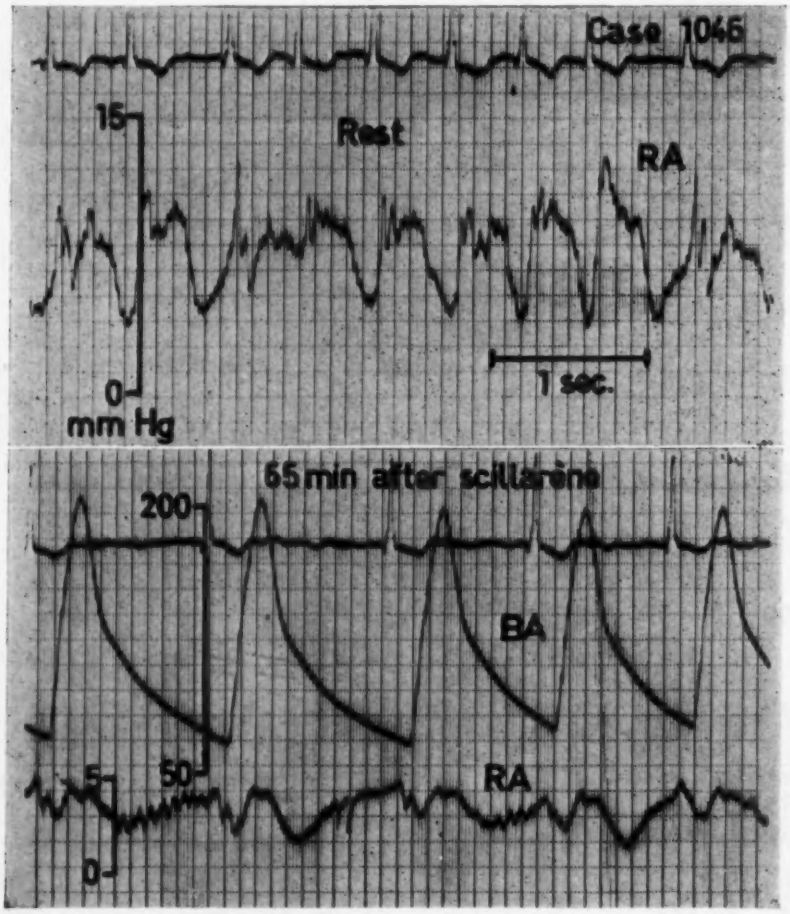


Fig. 3.—Right atrial pressure before, and 65 minutes after, 0.5 mg. Scillaren B intravenously, in Case 1046, with mitral stenosis, tricuspid incompetence, and rapid fibrillation.

The stroke volume was markedly increased as soon as 10 minutes after Scillaren had been given and rose somewhat during the next 20 minutes.

Fig. 1 shows the result of two studies in the same patient, 4 years apart, during which time the patient developed auricular fibrillation and increased incapacitating symptoms. In the first study the patient was given 1.2 mg. lanatoside C; in the second, 1.0 mg. Scillaren B. The different effect on the performance of the heart is readily seen.

Figs. 2 and 3 show typical pressure tracings.

TABLE III. HEART RATE BEFORE, AND DURING THE FIRST MINUTES AFTER, THE ADMINISTRATION OF 0.5 TO 1.0 MG. SCILLAREN IN 5 PATIENTS WITH RHEUMATIC HEART DISEASE

CASE NUMBER	RHYTHM	MINUTES BEFORE SCILLAREN					MINUTES AFTER SCILLAREN						
		30	20	10	5	½	½	1-2	3-6	9-11	20	30	50
1044	AF	84	82	87	79	86	83	78	81	80	81	80	79
1046	AF	109	113	88	103	93	86	89	79	78	65	59	59
1049	AF	92	88	85	86	90	84	75	74	77	61	58	50
1050	AF	119	113	132	113	106	96	118	96	95	71	67	70
Mean	AF	101	99	98	95	94	87	90	83	83	69	66	65
1051	SR	83	83	74	73	74	75	72	78	66	65	63	58

DISCUSSION

Since the development of heart catheterization technique, several studies have been published regarding the effect of different cardiac glycosides on the human heart. Digoxin, lanatoside C, and ouabain have been studied in relation to their effect on the normal, failing, or rheumatically altered human heart.[1-4] Most authors have not taken into account the fundamental difference between the pulmonary circulation of patients with valvular mitral stenosis and those with left ventricular failure, or the difference in the mechanism resulting in elevated right atrial pressure in tricuspid stenosis and in right heart failure. In stenosis of the atrioventricular valves, the filling of the ventricles is dependent on the heart rate, a slower rate giving longer diastolic time for filling with lower atrial pressure, and a more rapid rate shorter time for filling of the ventricles with higher atrial pressures. In patients with mitral and tricuspid valvular disease, when the administration of digitalis gives a marked slowing of the heart rate, it may be impossible to assess whether any strengthening of the myocardium has occurred also. In the present investigation, as in an earlier one,[4] only patients with predominant mitral stenosis in different stages of left or right heart failure have been studied.

From the results of this study it is clear that Scillaren is a rapidly active cardiac drug, especially in patients with auricular fibrillation. In some patients the action on the heart could be registered within one minute after its administration.

The elevated blood pressures both in the right atrium and in the pulmonary artery decreased rapidly when the drug was given. This decrease may be a consequence of the slower rhythm, since the elevation presumably was due more to the mechanical factor of valvular deformity than to myocardial failure.

With the decrease in pressure the stroke index rose, in some patients to double the initial value. It is impossible to determine from our data whether this was due primarily to the slower heart rate or to the effect of the drug on the myocardium. The increase in stroke volume was noted as early as 10 minutes after the administration of the drug. This finding confirms that Scillaren acts rapidly.

It has been claimed that Scillaren, besides its digitalis-like effect on the heart, also acts as a direct diuretic. Lanatoside C has been shown to exert a direct renal effect in patients with mitral valvular disease.[4,11] Digoxin has also a direct renal action, as demonstrated in animal experiments.[5] The present study was started in order to compare the action of lanatoside C to the supposedly diuretic action of Scillaren. It shows conclusively the lack of any direct renal effect of Scillaren, in contrast to lanatoside C and digoxin.

SUMMARY

1. The effect of a single intravenous dose of Scillaren B on the blood pressures in the lesser circulation, and the clearance values for inulin and para-aminohippurate as well as sodium excretion were studied in six patients with rheumatic heart disease.

2. Heart rate rapidly decreased, in some cases during the first minute after administration.

3. Pulmonary blood pressures fell rapidly, while cardiac output remained unchanged. Stroke index rose considerably.

4. No effect on clearance values or sodium excretion was noticed.

5. Compared with lanatoside C, Scillaren B acts with shorter latency on pulmonary pressures in patients with mitral stenosis, but does not show any of the prompt, direct renal effects of the digitalis drug.

6. Scillaren B is a swift and potent cardiac drug. The renal action which has been described earlier is secondary to its effect on the heart.

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COMPLETE TRANSPOSITION OF THE AORTA. LEVOPOSITION OF THE PULMONARY ARTERY WITH PULMONARY STENOSIS

Clinical and Pathologic Findings in Three Cases

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THE partial transpositions of the large vessels with levoposition of the pulmonary artery was described by Taussig and Bing.[1] Other cases[2,3,4] have been reported and there are additional ones in existence, in which the levoposition of the pulmonary artery is accompanied by pulmonary stenosis. We have had the opportunity of seeing 4 cases of this type at autopsy. One of those has been excluded here by reason of its association with a congenital tricuspid stenosis which gave it a clinical aspect different from that of the other 3.

Although when considered from the nosological point of view, both types of partial transposition are very similar, they offer ample differences when considered from the physiopathologic and clinical points of view. The fundamental difference lies in the fact that, while in the Taussig-Bing syndrome there is an increase of the pulmonary flow, in the malformation that we are referring to, a diminished pulmonary flow has been verified. This gives rise to the fact that this malformation resembles more closely the tetralogy of Fallot and the other types of transposition of the aorta with pulmonary stenosis than it does the Taussig-Bing syndrome.

In an intermediate position could be placed those cases of the Taussig-Bing syndrome that clinically have a diminished pulmonary flow, but in which autopsy does not reveal the presence of pulmonary stenosis. To this type corresponds the first of the two cases published by van Buchem and associates,[5] one having been proved by autopsy; and a more recent one published by Dubourg and associates,[6] which also was verified at autopsy. Van Buchem and associates pointed out a functional pulmonary stenosis in order to explain this discrepancy.

The diagnosis of this type of partial transposition with pulmonary stenosis is of more than academic interest since this malformation quite often resembles the tetralogy of Fallot (Campbell and Suzman's case and our own Case 3), and cases are frequently submitted to an aortic-pulmonary anastomosis of the Blalock or Potts' type, which proves fatal to the patient. This occurred in our 3 patients and in the few cases that we have been able to find in the literature.[2-7] The same occurred in the case of Dubourg and associates.

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CASE REPORTS

Case 1.*— G. P., a girl aged 17 years, was seen in 1948. She had had cyanosis since birth, and dyspnea on effort. There was no squatting; and she did not suffer from syncope. When she was 14 years old, she had had an hemoptysis.

Physical Examination.—She was a well-developed and well-nourished girl, with an accentuated scoliosis of the spine, and presenting severe and generalized cyanosis, with moderate clubbing of the fingers. A rough systolic murmur was audible, loudest in the third left intercostal space and in the pulmonary area. The second sound was clear after the murmur. The systolic arterial pressure was of 90 mm. Hg, without heart failure.

The fluoroscopy showed a moderately enlarged heart, with clear lung fields. The aorta proved to be right-sided, after esophageal opacification, and seemed very large. The ascending, as well as the descending, aorta were easily distinguishable, the latter forming a prominence in its lower supra-auricular portion. The pulmonary bay was concave, and the pulmonary branches, thin without pulsations. In the left oblique position, there was a large and clear pulmonary window. Right ventricular hypertrophy was present in the transverse position.

The ECG showed no axis deviation, with ventricular complexes of low voltage, RS_1, RS_2, and rS_3, in the standard leads. Unfortunately, no precordial leads were taken. The red cell count was 6,070,000, with 102 per cent hemoglobin.

Operation was decided upon and a Blalock-Taussig anastomosis on the left side was performed, on July 13, 1948, by Professor Santy. However, she remained cyanotic after the operation, and finally died of pulmonary edema 8 days later.

Necropsy.—There was complete transposition of the aorta; infundibular pulmonary stenosis. The pulmonary artery overrode the high ventricular septal defect. The aortic orifice arose from the extreme right portion of the right ventricle. The aortic circumference was 8 cm. just below the aortic cusps. Pulmonary circumference at the main trunk was 5 cm. There was preinfundibular pulmonary stenosis, with 4 mm. diameter. There were only two pulmonary valve cusps: right posterior and left anterior. The thickness of the right ventricle was 12 mm., as compared with the 15 mm. of the left ventricle. The right ventricle communicated with the left through a large, high, interventricular septal defect, 30 mm. in diameter, which was semilunar in shape. The two atria communicated well via a patent ostium primum, 13 mm. in diameter. The anastomosis was quite permeable, with a diameter of 5 mm.

Case 2.—J. G. was a 2-year-old male. He was a blue baby from birth. The infant had not walked, but used the squatting position in his bed. After 1 year of age, he often presented syncopal attacks. The physical examination revealed a generalized cyanotic patient, with clubbing of the fingers and toes. The femoral pulse was strong; the systolic pressure was 11/? mm. Hg. There was a systolic murmur Grade 3 in the pulmonary area, without thrill; the murmur was heard also in the back.

The ECG (Fig. 1) showed an hyperdeviated right electrical axis of the S_1, S_2, and R_3 type as well as evidence of a right ventricular hypertrophy in the extreme right thoracic leads and in V_1, with an inverted T wave in the same leads. The electrical diagnosis was a right ventricular hypertrophy of the adaptation type.

At fluoroscopy, the lung shadows were clear. The heart was already of increased size, considering the child's age (Fig. 2). An angulation between the aorta and the left border of the heart was seen; underneath the aorta, a shadow was discovered (it being fainter) that could have been a left superior vena cava. In the transverse position, hypertrophy of the right ventricle was observed. In the left oblique position, the aorta was very large. The pulmonary window was not very clear. The aortic arch was left-sided. The angulation between the aorta and the heart's anterior border was usual. The red cell count was of 6,380,000, with 102 per cent hemoglobin.

An angiocardiogram showed (1) an early aortic opacification, without filling of the pulmonary artery, (2) the existence of a superior vena cava, and (3) the absence of a levogram.

A Potts' anastomosis was performed on Sept. 21, 1954, by Professor Santy. The cyanosis was not relieved in spite of the operation, and on the following day there was evidence of cere-

*For the sake of brevity, illustrations belonging to Cases 1 and 3 have been omitted.

brovascular damage, together with congestive heart failure. In view of this condition, it was decided to carry out the ligation of the inferior vena cava, and this was done on Oct. 1, 1954. The infant improved greatly, but he remained cyanotic, and 27 days later a new episode of cerebral thrombosis and congestive heart failure made its appearance. The infant's condition improved with heparin and digitalis, and the closure of Potts' anastomosis was then decided upon. The patient died the day after operation.

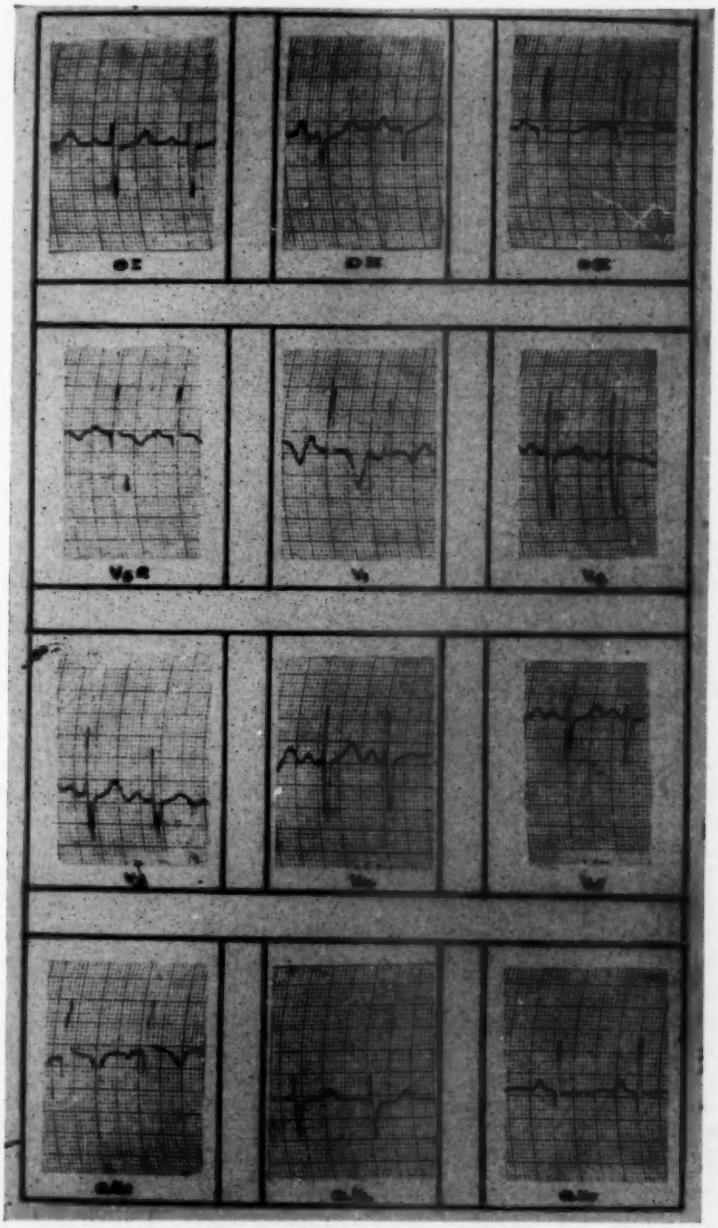

Fig. 1.—Case 2. Electrocardiogram.

Autopsy of the Heart.—(Dr. Bret; Figs. 3 and 4.) There was transposition of the aorta, with levoposition of the pulmonary artery riding on the high ventricular septal defect: in short, a

Taussig-Bing complex, with pulmonary stenosis, besides. A fibromuscular band came from the mitral valve and lead in to the ventricular cavity, going through the ventricular septal defect, thus reducing its surface area. The atria were extirpated, and it was not possible to ascertain anything about the venous return. The aortic orifices had 3 valves; the pulmonary was found to have only 2. The constriction was found to be of the subvalvular type. There was a patent foramen ovale. The left ventricle was 13 mm. thick; the right ventricle, 10 mm. thick. The circumference of the aorta measured 50 mm.; that of the pulmonary artery, 25 mm. The pulmonary stenosis was 4 mm., and the right atrium was larger than the left one.

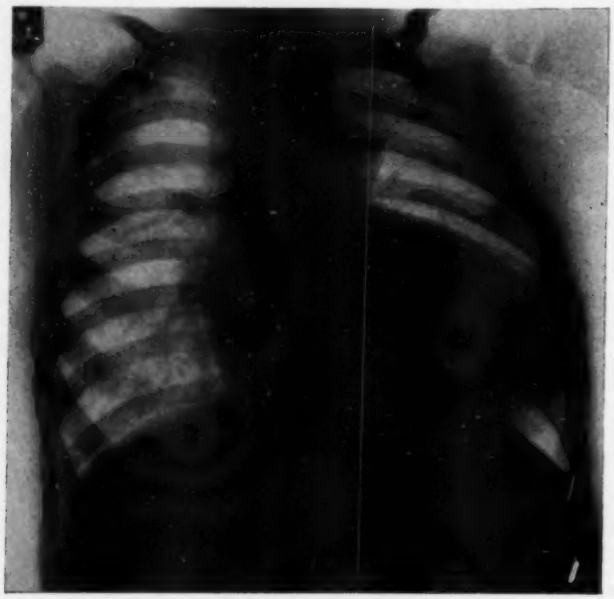

Fig. 2.—Case 2. Teleroentgenogram of the heart in the posteroanterior view.

Case 3.—B. M. was a boy aged 5½ months. He had had cyanosis from the time of birth. It had diminished, but never disappeared. He was not affected by syncope, but a marked dyspnea appeared after crying. The physical examination showed a generalized cyanosis. There was no squatting. A systolic murmur was audible in the third left intercostal space, it being also heard in the back. Radial and femoral pulsations were vigorous. At fluoroscopy, the heart was moderately enlarged, with a marked angulation at the level of the pulmonary conus. The pulmonary arteries were not visible. The lungs and pulmonary window were found clear. The aorta was of large size. There was a moderate angulation between the aorta and the anterior border of the heart, in the left oblique position, with left-sided aortic arch (esophageal opacification). The ECG showed an hyperdeviated right axis, of the S_1, S_2, and R_3 type, and a pattern of right ventricular hypertrophy of the adaptation type. The red cell count was of 5,000,000, with 80 per cent hemoglobin. Everything pointed to a diagnosis of the tetralogy of Fallot, with the exception of the cyanosis from the time of birth and the hyperdeviated axis. A Potts' anastomosis was performed on Sept. 27, 1955, by Professor Santy, and the infant did not wake up from anesthesia; he died a few hours later.

Autopsy.—There was complete transposition of the aorta, with partial transposition of the pulmonary artery riding on a high interventricular septal defect; valvular pulmonary stenosis of 2 mm., with only two cusps; and juxta-aortic remainder of the ductus arteriosus. There was a normal venous return, the right atrium being of larger size than the left. The foramen ovale was not patent. The auriculoventricular orifices were normal. Thickness of the right ventricle was 9 mm., and of the left, 8 mm. Circumference of the aorta was 33 mm. Potts' anastomosis was permeable only 1 mm.

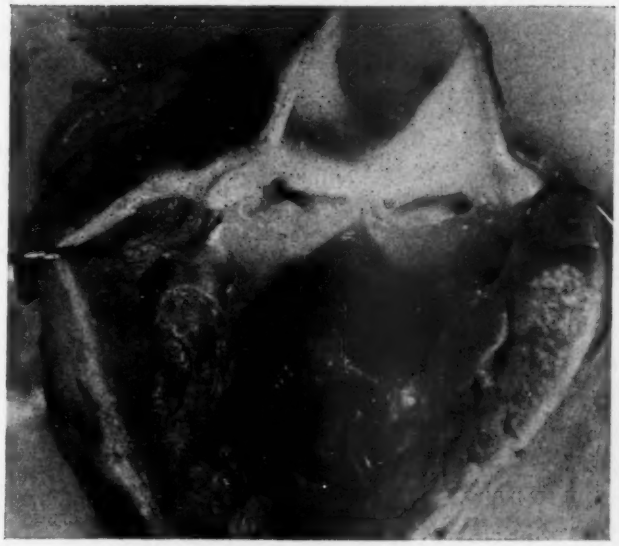

Fig. 3.—Case 2. Right ventricular view showing origin of the aorta.

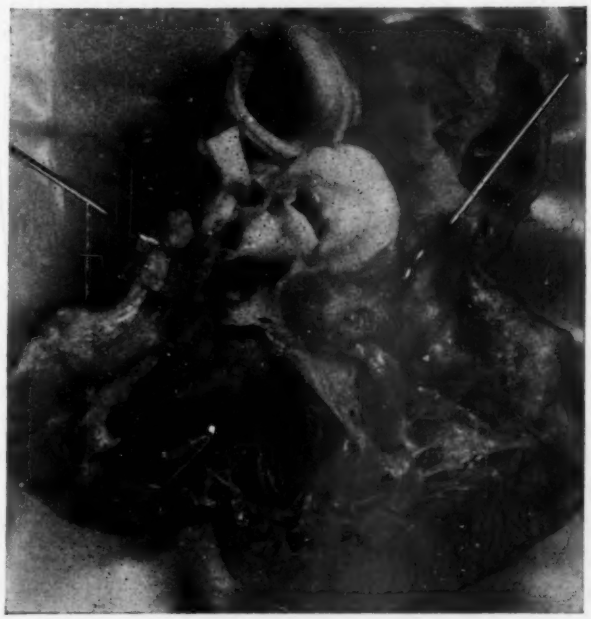

Fig. 4.—Case 2. Left ventricular view showing the high ventricular septal defect transversed by a fibrous band. The suborificial pulmonary stenosis appears just above the ventricular septal defect.

DISCUSSION

In accordance with the *anatomic* point of view, the findings have been similar in the three observations, verifying the following facts: a complete transposition of the aorta, which emerged entirely from the right ventricle; a pulmonary artery overriding a high interventricular septal defect; a pulmonary valve with

only two cusps; subvalvular, preinfundibular or valvular pulmonary stenosis; right ventricular hypertrophy; left ventricular hypertrophy (Case 1); a patent foramen ovale (Case 2), and closed (Case 3). In Case 1, there was a large atrial defect of the "ostium primum" type.

Clinically, the three cases were characterized by early cyanosis, which appeared right after birth; and the systolic murmur of a moderate intensity, without thrill, in the pulmonary area, with audible second sound (aortic component) in the same area. The femoral and radial pulsations were vigorous, with absence of episodes of cardiac insufficiency. The functional capacity was notably deficient.

Radiologically, the heart was found to be of a size somewhat larger than in the tetralogy of Fallot, showing in a frontal position a clear angulation between the aorta and the inferior left cardiac border; and to have a large aorta, with a left aortic arch (Cases 2 and 3), or a right one (Case 1). The pulmonary circulation was diminished, with clear lung fields and absence of hilar pulsations. The pulmonary window was clear. In the left oblique position there was an hypertrophy fundamentally of the right ventricle, with a correct angulation between the aorta and the anterior border of the heart. Two of our cases had a complete *electrocardiographic* study. The findings are common to both cases, and they consist in the presence of an hyperdeviated electrical axis to the right, of the S_1, S_2, and R_3 type. The precordial leads showed the pattern of right ventricular hypertrophy of the adaptation type. In Case 1, only the standard leads were registered, and a clear right axis deviation was not evidenced. It may be that this fact was due to the anatomic finding of a biventricular hypertrophy. Only in Case 2, was there an *angiocardiographic* study, in which there was demonstrated an early opacification of the aorta, and the absence of any filling of the pulmonary arteries, as much in the first exposures as in the last ones.

Surgical Results.—In spite of the fact that the reported clinical data of our 3 cases could not be exactly indicative of the tetralogy of Fallot, the operation was decided upon, after some hesitation, by reason of the diminution of the pulmonary flow. In Cases 2 and 3, an anastomosis of the Potts' type was performed, and in Case 1, a Blalock-Taussig operation was carried out. In the 3 cases, cyanosis persisted after surgery. In Cases 1 and 2, it did appear, moreover, that a picture of cardiac insufficiency caused the patient's death. In Case 1, death was caused by pulmonary edema, the sixth day after operation. In Case 2, an attempt was made to correct the heart failure by means of the ligature of the inferior vena cava, with the patient dying after a third intervention (closure of Potts' anastomosis). Case 3 died the day after operation.

After examination of the anatomic picture, it is not difficult to explain the cause of the unsuccessful operative results. The complete transposition of the aorta, with its emergency orifice far away from the interventricular septal defect, together with the riding pulmonary artery with pulmonary stenosis, must have rendered difficult the evacuation of the left ventricle, with did not resist the overburden established by the anastomosis. In the case of Campbell and Suzman,

too, death came 24 hours after performing the anastomosis. The cases of Donzelot and associates, and the one reported by Dubourg and associates, also died after operation. In the last case, however, pulmonary stenosis was not found in the necropsy study.

It is quite difficult to establish a living average of this malformation, inasmuch as death occurred by consequence of the operation performance in all the cases that we know of. One of our cases was 17 years of age; Campbell's was 24; in the two cases large septal defects existed. Perhaps this fact may explain the longer survival. In our other two cases the malformation was so badly tolerated that it is difficult to believe that, if the surgical treatment had not been carried out, they would have survived much longer.

Differential Diagnosis.—The differential diagnosis rests between (1) the tetralogy of Fallot, (2) complete transposition of the great vessels with pulmonary stenosis, and (3) complete transposition of the aorta, with the pulmonary artery coming out from the right ventricle, with pulmonary stenosis. In regard to the diagnosis, it is convenient to separate, on the one hand, the tetralogies of Fallot with early cyanosis, from the most complex group of transpositions of the aorta with pulmonary stenosis, in which the performance of an aortic-pulmonary anastomosis has undesirable consequences. Three types can be distinguished in accordance with the location of the pulmonary orifice: (1) coming out from the right ventricle, (2) riding pulmonary artery, or (3) pulmonary artery totally transposed. The distinction between these three types is really difficult, although from the practical point of view, the interesting feature is the differentiation from the tetralogy of Fallot. Cyanosis from time of birth is a good indication of the transposition of the aorta, but, in accordance with our own experience, it can be seen also in some of the Fallot tetralogies. In these cases, the electrocardiogram aids the most in the differentiation. The aspect of the precordial leads is of lesser interest in this particular case than is the study of the electrical axis in the standard leads, since the aspect of right ventricular hypertrophy of the adaptation type (right ventricular hypertrophy pattern in the right precordial extreme leads and V_1) is as common in the tetralogy as in the three types of the transposed aorta with pulmonary stenosis. On the contrary, the axis deviation in the standard leads shows some differences: In Fallot's tetralogy the QRS axis deviation is usually of the S_1, R_2, R_3 type, and in some instances also of the S_1, S_2, R_3 type, but it very rarely shows a S_1, S_2, S_3 pattern, whereas in the different types of transposition of the aorta with pulmonary stenosis, mentioned above, the rule is to find a QRS axis deviation to the right of the S_1, S_2, R_3 or S_1, S_2, S_3 types, while the aspect S_1, R_2, R_3 is not very usually seen.

Worthy of note is the fact that in two of our cases of transposition of the aorta with riding stenotic pulmonary artery, the pattern S_1, S_2, R_3 was showing up precisely. Further observations will be necessary to correlate the type of the QRS axis deviation and the position of the pulmonary artery orifice. The value of the presence of cyanosis right after birth, associated with a right axis deviation of the type S_1, S_2, R_3, for the diagnosis of this malformation, has been corroborated by its presence in other cases in the literature.[7]

TABLE I. CLINICAL DATA

CASES	CYANOSIS	SQUATTING	SYNCOPES	PULMONARY INFECTIONS	F.C.	HEMOPTYSIS	MURMUR	SECOND SOUND PULMONIC AREA	C.I.	F.P.
1. G. P. 17 yr.	Since birth	No	No	No	Fair	Once; with grip	Systolic pulm. & 3rd intercostal space; no dorsal propagation	Quite patent	No	Good
2. J. G. 2 yr.	Since birth	Yes	Yes	No	Very bad	No	Systolic pulm., without thrill. 2nd intercostal space maximum bilateral—dorsal propagation	?	No	Good
3. B.M. 5½ mo.	Since birth	?	No	No	Very bad; fatigue after crying, very accentuated	No	Without thrill; dorsal propagation. 2nd intercostal space maximum	?	No	Vigorous

F. C. = Functional capacity; C. I. = Cardiac insufficiency; F. P. = Femoral pulsation.

TABLE II
Radiologic Data

CASES	HEART SIZE	LUNG SHADOWS	ANGULATION (IN MIDDLE ARCH SITE)	AORTIC ARCH	PULMONARY WINDOW	RVH
1. G. P.	Medium	Clear; no hilar pulsations	Yes	Right-sided, and very large	Very clear	Evident
2. J. G.	Large	Clear; no hilar pulsations	Yes	Left-sided, and very large	Not very clear	Evident
3. B. M.	Medium; not large	Clear; no hilar pulsations	Yes	Left-sided, and very large	Clear	Light

Electrocardiographic Data

CASES	AXIS DEVIATION	RVH
1. G. P.	Undifferentiated; RS_1, RS_2, and rS_3	No precordial leads
2. J. G.	To the right; S_1, S_2, and R_3	Of the adaptation type
3. B. M.	To the right; S_1, S_2, and R_3	Of the adaptation type

RVH = Right ventricular hypertrophy.

TABLE III. POSTOPERATIVE COURSE AND AUTOPSY

CASES	OPERATION	RESULTS	TREATMENT	CYANOSIS	DEATH	AUTOPSY
1. G. P.	Left Blalock (right aortic arch)	Heart failure; pulmonary edema	Digitalis	Persisted after the operation	At the 6th day	Transposition of the aorta. High VSD, Preinfundibular pulmonary stenosis. Riding pulmonary. 2 pulmonary cusps. Large ASD. Left ventricle with greater thickness than the right one.
2. J. G.	Potts	Severe heart failure, with neurologic trouble	Vena cava ligature; heparin and digitalis	Persisted after the operation	At the Potts' closure; 39 days after 1st operation	Transposition of the aorta, pulmonary artery overriding the high VSD, and suborificial pulmonary stenosis. 2 pulmonary cusps. Patent foramen ovale
3. B. M.	Potts; bad; pulmonary artery was very much reduced	Total pneumothorax, on left side		Persisted	The day after operation	Transposition of the aorta. High VSD. Riding pulmonary. Orificial pulmonary stenosis. 2 pulmonary cusps. No patent foramen ovale

VSD = Ventricular septal defect; ASD = Atrial septal defect.

SUMMARY

Three cases of transposition of the aorta, with levoposition of the pulmonary artery and pulmonary stenosis, are clinically and pathologically reported.

This malformation resembles more closely Fallot's tetralogy than the Taussig-Bing syndrome, due to the fact that it shows a diminished pulmonary blood flow.

The combination of cyanosis, appearing right after birth, associated with a right axis deviation in standard leads of the S_1, S_2, and R_3 type is, in the authors' opinion, an important clue for suggesting the diagnosis, as it is rarely seen in Fallot's tetralogy.

Our 3 cases were operated upon by means of an aortopulmonary anastomosis. The operation was followed by death in all cases, within a short period of time, without relief of the cyanosis, and leading also to heart failure.

From the anatomic point of view, besides the complete transposition of the aorta, the levoposition of the pulmonary artery riding over a high ventricular septal defect, a pulmonary stenosis was found. The pulmonary orifice was guarded with only two cusps in all 3 cases; and in 2 cases a patent foramen ovale or an atrial septal defect also was found.

The differential diagnosis with Fallot's tetralogy has been emphasized.

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THE NORMAL DIRECT SPATIAL VECTORCARDIOGRAM

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CRITERIA for definite diagnosis of borderline cardiac abnormalities using direct spatial vectorcardiographic techniques are practically nonexistent because of the relatively small number of normal cases heretofore studied and reported.

A survey of the literature produces comparatively few reports in English-language journals. Elek, Allenstein, and Griffith,[1] using the Duchosal-Sulzer cube electrode placement as modified by Grishman and his co-workers,[2] described vectorcardiograms of 47 normal infants under 2 years of age. Lamb and Dimond,[3] using their own reference system, reported on 46 normal children in the first decade of life. Scherlis, Lasser, and Grishman[4] described vectorcardiograms of 62 normal patients—21 under 20 years of age, and 2 over the age of 70; and Lowe and Goble[5] reported on 104 normal patients, 5 to 75 years of age, employing their modification of the Duchosal-Sulzer placement for most of the study, but also including observations using the triangular placement of Arrighi. Using the tetrahedron reference system, Conway, Cronvich, and Burch[6] studied 16 normal medical students; Burch, Abildskov, and Cronvich[7] described vectorcardiograms of 75 normal adults between the ages of 22 and 33; and Abildskov[8] described vectorcardiograms of 114 normal adults between the ages of 40 and 73 years. In all, a total of less than 500 normal cases have been reported, infants included.

Because of variations among reference systems employed, and because of the few cases reported, a considerable zone remains between definitely abnormal vectorcardiograms and those incontrovertably normal. Admittedly, the transition from normal to abnormal, pathologically and physiologically, may be so gradual as to defy detection; nevertheless, advancement in cardiac diagnosis demands narrowing of this zone insofar as possible.

In this paper we add to the literature a report on 100 patients with presumably normal hearts, thereby supplying additional detail to the understanding of the normal vectorcardiogram. Grouping by decades aids in clarification of changes with age.

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SELECTION OF PATIENTS

The 100 patients singled out for this study from among hospitalized patients at the Los Angeles County Hospital were free from cardiac pathology, as confirmed by histories, physical examinations, electrocardiograms, chest x-rays, and, in some cases, cardiac fluoroscopy. (Patients with qR or rsR′ configurations in right precordial ECG leads were excluded from the study.) Distribution of patients is shown in Table I.

TABLE I. DISTRIBUTION OF PATIENTS

AGES	MALES	FEMALES	TOTAL NUMBER
10–19	9	5	14
20–29	11	13	24
30–39	7	5	12
40–49	5	4	9
50–59	7	2	9
60–69	6	5	11
70–79	6	7	13
80 and over	2	6	8

METHODS

Vectorcardiograms were taken using the cube electrode placement of Duchosal and Sulzer as modified by Grishman and associates. In our early studies a single oscilloscope was used, so arranged that each plane could be viewed with push-button rapidity. More recently we have employed a three-scope vectorcardiograph, permitting simultaneous viewing of all three planes. Vector loops were interrupted by intensity modulation, permitting time analysis. Segments were tapered, the pointed end indicating direction of movement of the loops. The time interval usually was 400 per second, although some studies were made at 360 per second, and many others at 200 per second in order to permit study of the T waves. A permanent record was obtained by photographing the loops with a camera employing fast film and time exposure.

Electrical positions were determined on the vectorcardiogram by applying the long axis of the frontal loop against the triaxial diagram of Bayley.[9] Using the electrocardiogram, position was determined by the method of Goldberger,[10] using augmented unipolar limb leads.

Fig. 1.—**Orientation of spatial vector loops in the various planes. This reference system will apply to all subsequent illustrations.**

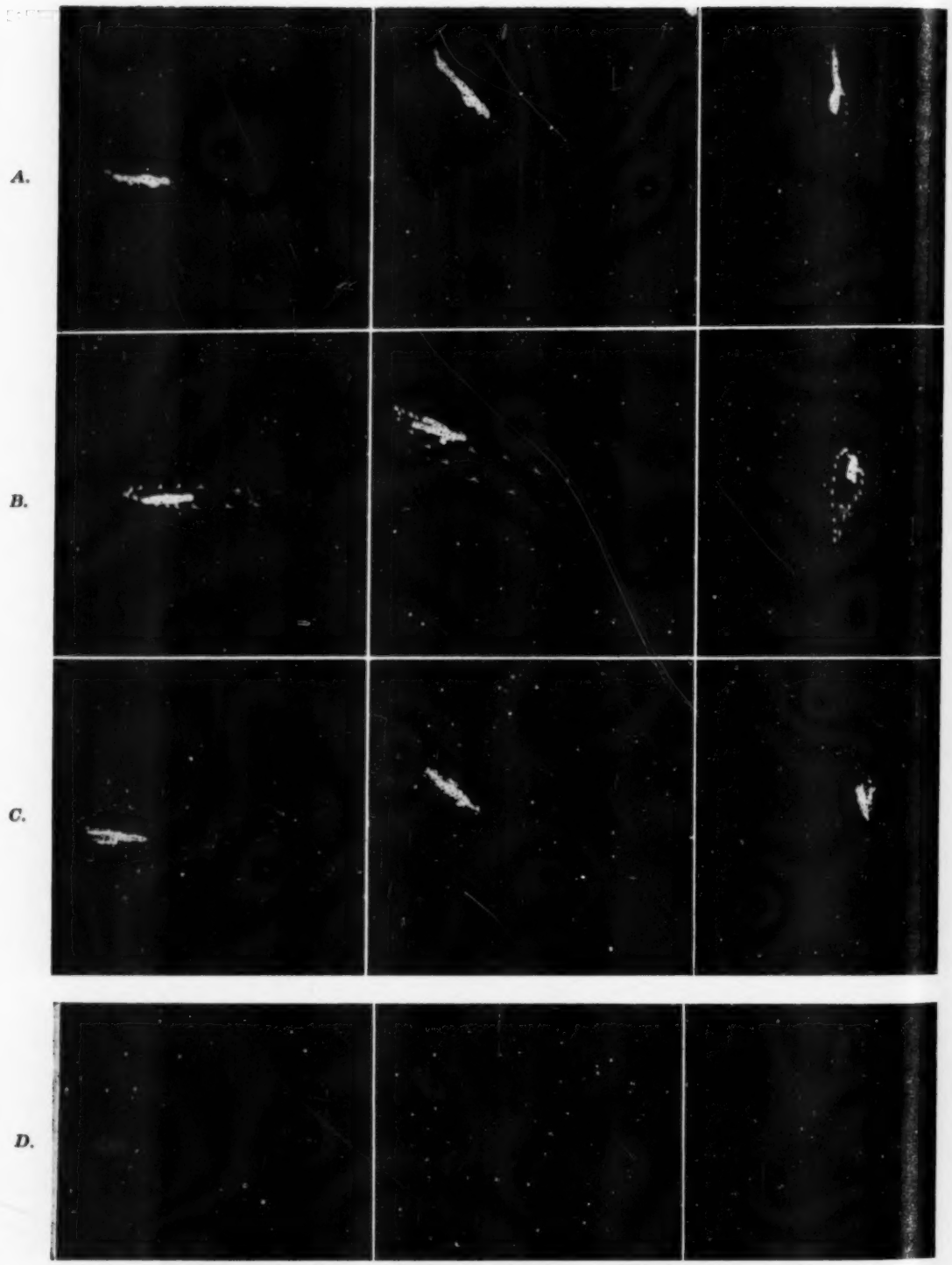
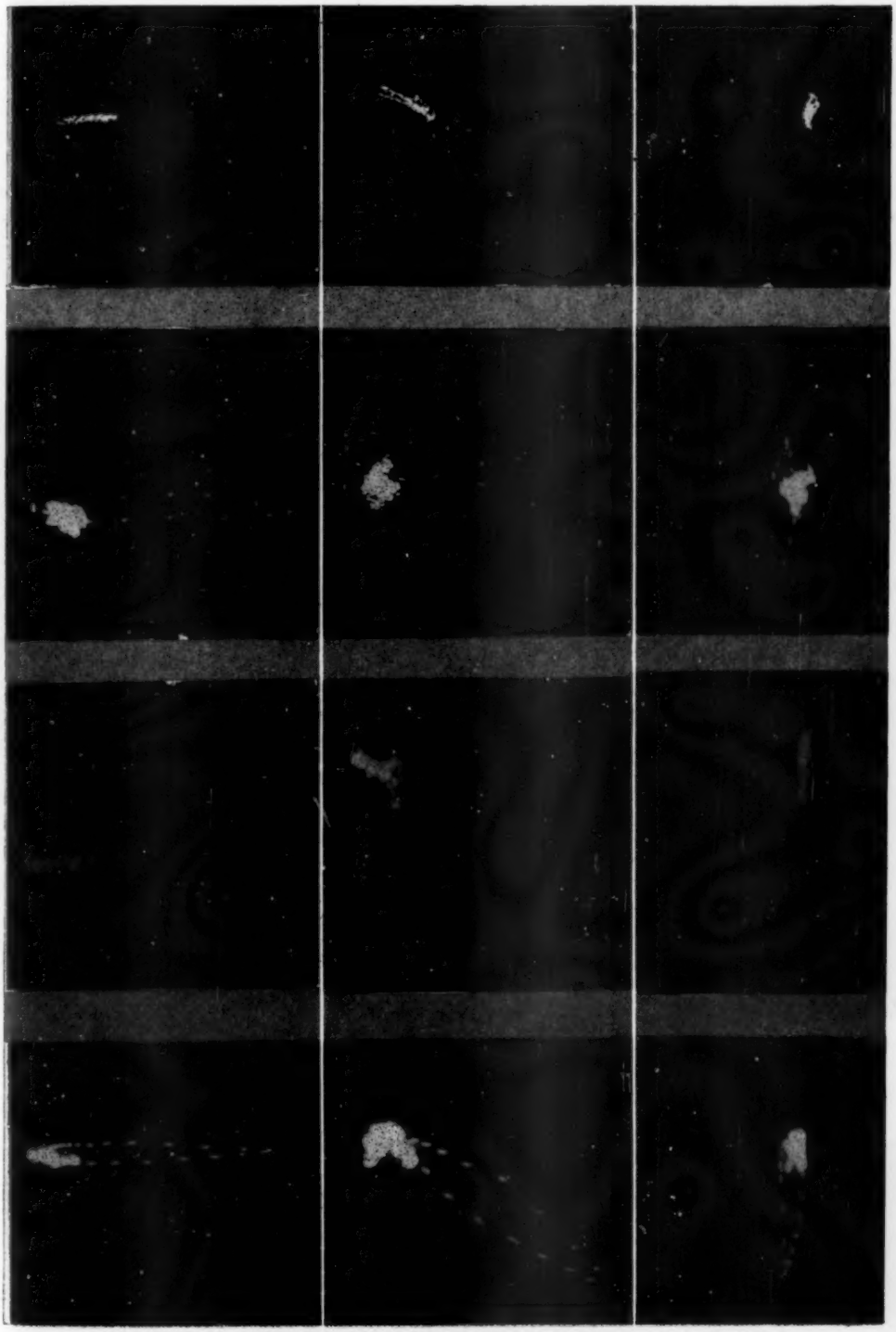


Fig. 2.—Typical normal vectors for each age group. *A*, Age 10-19. *B*, Age 20-29. *C*, Age 30-39. *D*, Age 40-49. *E*, Age 50-59. *F*, Age 60-69. *G*, Age 70-79. *H*, Age 80 or over.



E.

F.

G.

H.

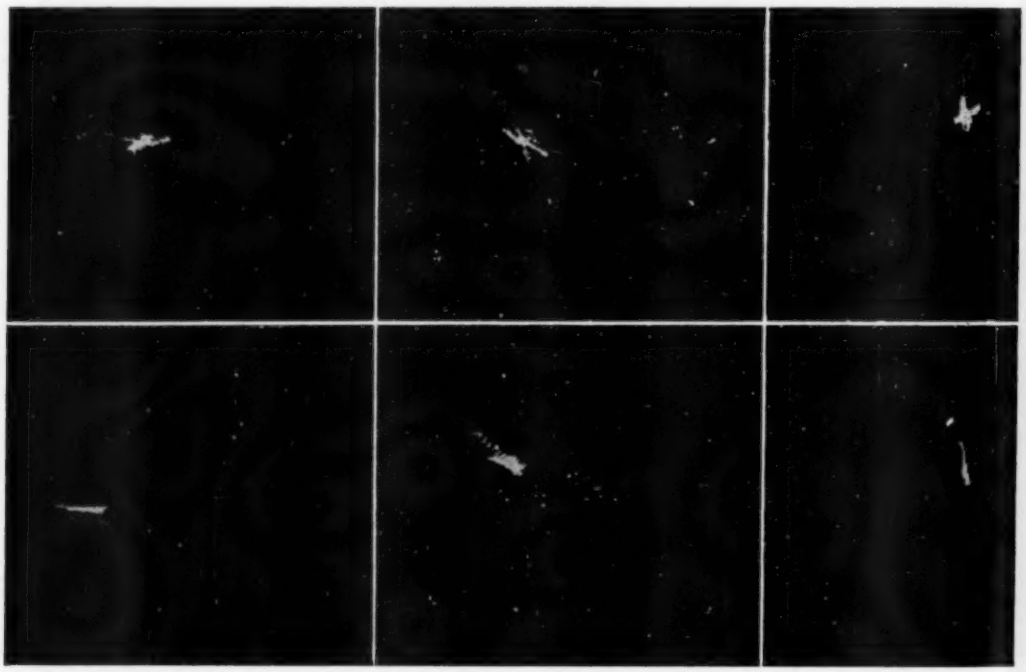
(Fig. 2,E-H. For legend see opposite page.)

OBSERVATIONS

Characteristics of vectorcardiograms in this series follow. Some of the features mentioned have been described previously.[1,3,4,5,6,11]

I. *QRSsÊ.*—In all cases studied the QRSsÊ loop is closed, with the terminal portion returning to the E point. In general, all QRSsÊ loops start slowly anteriorly. Although the loop actually moves first to the right and then turns abruptly to the left, the rightward limb often is so small that, when photographed, the loop appears to move to the left immediately from its point of origin. This initial limb may originate somewhat superiorly, but more often is directed inferiorly from the onset. The loop progresses more rapidly (i.e., longer segments are seen) in its midportion—located in the posterior, left, inferior octant—and then returns with a slower (i.e., more closely spaced, with smaller segments) terminal portion to the E point, thus closing the loops (Fig. 2). Changes of rate and progression are smooth and gradual.

A.



B.

Fig. 3.—*A* and *B*, Normal orientation for age with prominent right posterior segment of QRSsÊ loop.

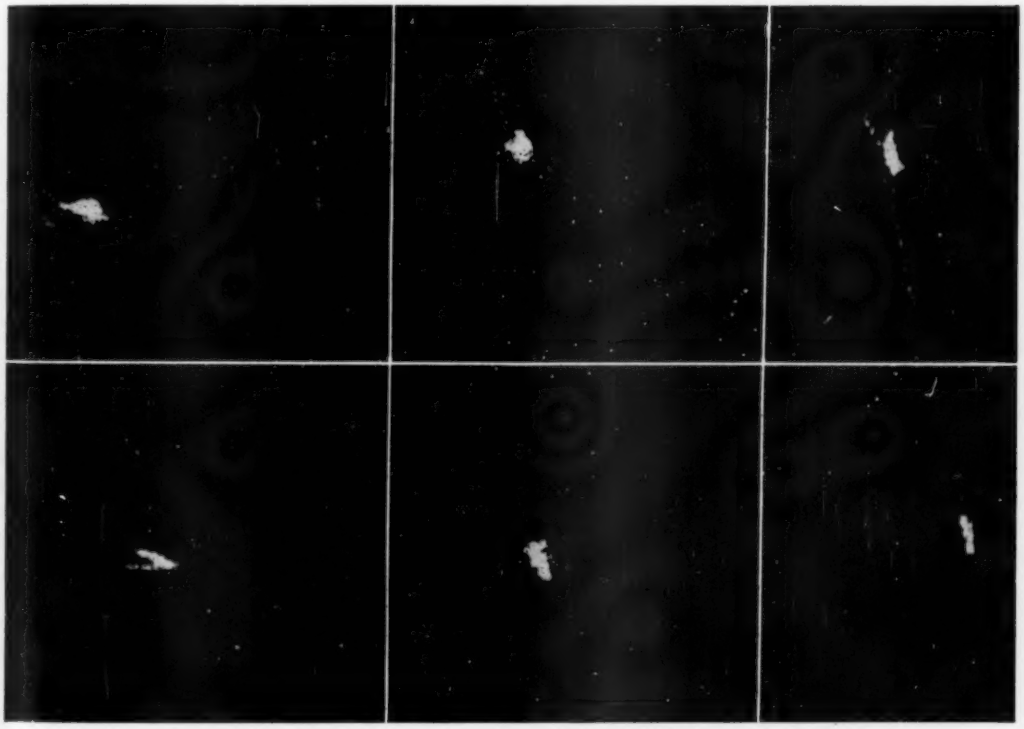
H *F* *S*

Fig. 4.—Anterior portion of QRSsÊ loop prominent, with normal orientation and a figure-of-eight in horizontal plane.

Age changes are noted in vector spatial orientation, the QRSsÊ loop lying more posteriorly with increasing age. In the youngest age group, QRSsÊ loops usually are located in the left inferior octant, predominantly anteriorly. Contrariwise, QRSsÊ loops in the oldest age group commonly lie in the left inferior posterior octant, with very little of the vector loop seen anteriorly. Between these extremes, a gradual transition of QRSsÊ-loop orientation is observed (Fig. 2,*A-H*).

In terms of individual views, the *horizontal view* consists of a counterclockwise loop to the left, with the initial portion anterior and part of the subsequent loop posterior to the E point (Fig. 2). Figure-of-eight loops in the horizontal plane are noted in 4 out of 14 patients between the ages of 10 and 19, and in 4 out of 24 patients between the ages of 20 and 29. No figure-of-eight loops are noted in age groups beyond the twenty-ninth year in our series. In all instances the proximal loop (to the E point) is counterclockwise in direction.

A.



B.

Fig. 5.—*A* and *B*, Moderately large superior portion with normal orientation as to anterior and posterior octants for the age.

H *F* *S*

Fig. 6.—Prominent posterior portion of the QRSsÊ in a young person.

The *sagittal view* reveals a clockwise loop, starting anteriorly, progressing inferiorly, and returning posteriorly. Occasional figure-of-eight loops are seen.

In the *frontal view* the loop, which is predominantly to the left and mostly inferior, is more variable in shape and direction of inscription (Table II). Direction of rotation shows no correlation with either long axis or electrical position.

TABLE II. DIRECTION OF INSCRIPTION OF FRONTAL LOOP

AGES	CLOCKWISE	COUNTERCLOCKWISE	FIGURE-OF-EIGHT
10–19	5	2	7
20–29	16	4	4
30–39	5	4	3
40–49	5	3	1
50–59	2	1	5
60–69	4	5	2
70–79	3	6	5
80 and over	0	8	0

A rough correlation exists between the electrical position as determined in the electrocardiogram and the electrical position as seen in the frontal plane. In the more vertical hearts, as determined in the electrocardiogram, the long axis of the QRSsÊ loop occurs between + 45 and + 90 degrees of the triaxial system in the frontal plane, while intermediate and horizontal heart positions lie between + 45 degrees and 0 degrees in the frontal plane. The long axis does not lie outside of the 0 to + 90 degree quadrant in any of the cases studied.

Variations in the vectorcardiograms which apparently follow no fixed pattern are observed throughout the age groups within this study. These are described here with suggested interpretations:

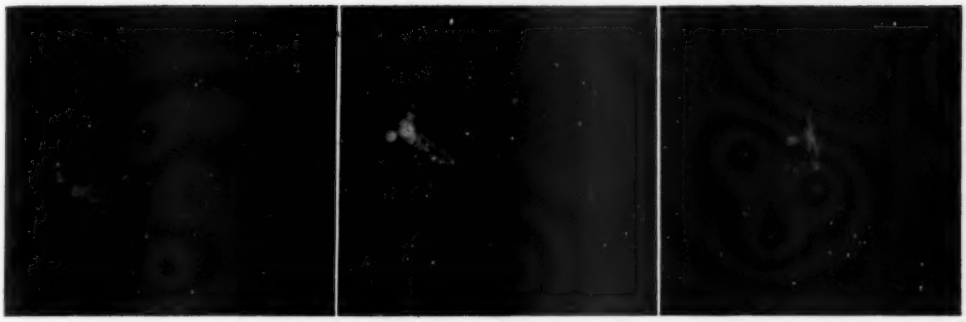
1. Normal orientation for age with prominent right terminal portion of the QRSsÊ—6 casse (Fig. 3,*A* and *B*). This vectorcardiographic variation is similar to incomplete bundle branch block in otherwise normal patients.[13] The RSR′ in right precordial leads was not seen in electrocardiograms of our patients, as the right terminal appendage is more posterior in patients in our series than in persons in whom the RSR′ pattern is found, presumably as a result of the anatomic and/or electrical position of the heart in such persons.

2. Figure-of-eight in the horizontal plane—1 case (Fig. 4). This pattern, noted in a 16-year-old patient, reportedly occurs in many persons under 10 years of age, less often between the ages of 10 and 20, and more rarely beyond the twentieth year.[3]

3. Moderately large superior portion with normal orientation as to anterior and posterior octants for the age—3 cases (Fig. 5). A prominent superior portion without posterior displacement is seen in these patients. This might be accounted for by peculiar positioning of the heart, possibly posterior tipping of the apex, which would throw the base of the heart more superiorly.

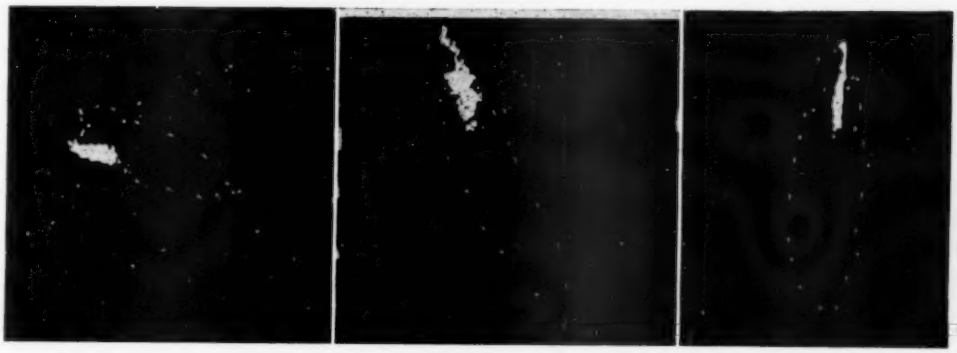
4. Prominent posterior portion of the QRSsÊ in a young person—1 case (Fig. 6). Because of the prominent posterior portion, this vectorcardiogram is consistent with older age. No obvious explanation for its occurrence in this 23-year-old woman is apparent.

5. Indentation in the posterior superior portion of the QRSsÊ loop—1 case (Fig. 7). Although this configuration suggests the possibility of an infarct[11] in the posterior superior portion, TsÊ loops are normal and no confirmatory evidence is found in past history or by other methods of examination.



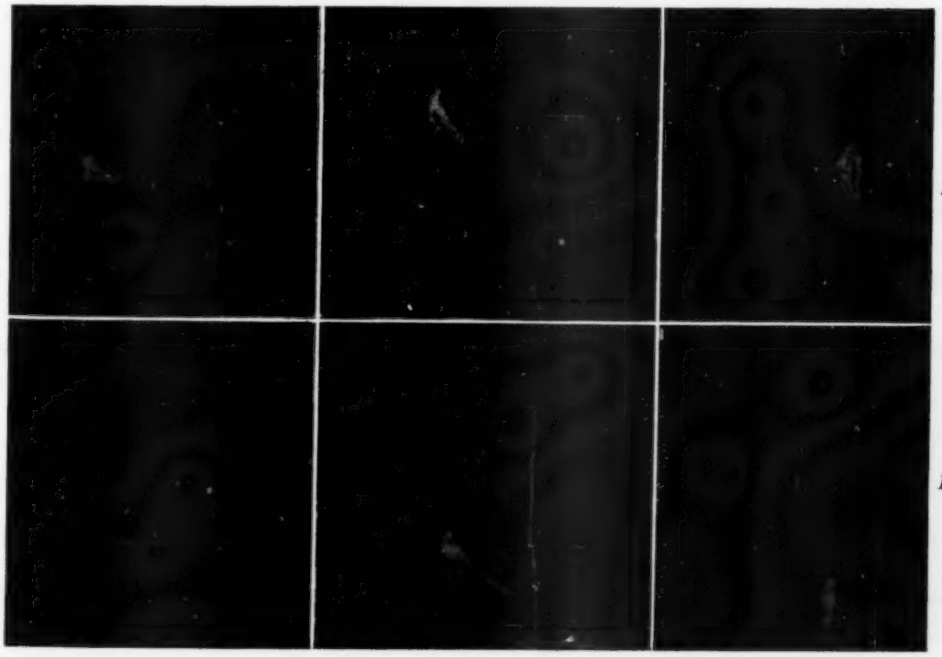
H *F* *S*

Fig. 7.—Indentation in the posterior portion of the QRSsÊ loop.



H *F* *S*

Fig. 8.—Slightly more anterior prominence than expected at older age.



A.

B.

Fig. 9.—*A* and *B*, Moderate posterior and marked superior displacement of QRSsÊ loop.

6. Slightly more anterior prominence than expected at older ages—2 cases (Fig. 8). The only apparent explanation for this unusual anterior location is a possible variation in anatomic position. In the illustrated case, the patient is 69 years old; the other patient with a similar configuration is 63 years of age.

7. Moderate posterior and marked superior displacement of the QRSsÊ loop—3 cases (Fig. 9,*A* and *B*). These vectorcardiograms are consistent with either left ventricular hypertrophy or, possibly, inferior or diaphragmatic infarct, despite absence of clinical evidence in support of these diagnoses. We suggest that these vectors may represent abnormalities not otherwise evident using present methods of diagnosis.

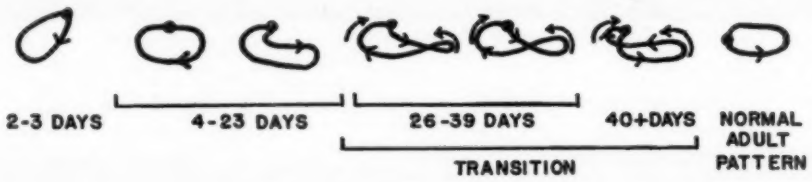


Fig. 10.—VCG transition from neonatal to adult pattern as seen in horizontal plane (schematic).

II. *TsÊ.*—In all planes, TsÊ loops rotate in the same direction as QRSsÊ loops. In all but 2 patients, one aged 26 years and the other 68 years, the TsÊ loops are enclosed within the QRSsÊ loops in all planes. In every instance, TsÊ loops form closed loops and appear to follow after the completion of the QRSsÊ loops. In general, the long axis of the TsÊ loop parallels closely the long axis of the QRSsÊ loop.

III. *PsÊ.*—Using our present equipment, PsÊ loops could not be observed in detail sufficient for accurate analysis.

DISCUSSION

In addition to variations described thus far, the following deserve special mention. When cases studied are divided into age groups by decades, a gradual change with age in the position of the QRSsÊ loops becomes apparent. With this trend in mind, typical octant relationships of the QRSsÊ loops for particular age groups are suggested: In newborn human infants, relative predominance of the right ventricle at birth produces a QRSsÊ pattern suggestive of right ventricular hypertrophy. At the age of 20 to 40 days, a shift toward the normal QRSsÊ occurs,[1] oriented in the left, anterior, inferior octant and resembling vectors seen in younger age groups within this series. In young adults, QRSsÊ loops are located to the left, either predominantly posteriorly and inferiorly, or midway between the posterior inferior octant and the anterior inferior octant. With increasing age, the loops assume a definitely more posterior position, with a tendency to occur in positions closer to the superior posterior octant, approaching the characteristic appearance of left ventricular hypertrophy, i.e., location of the QRSsÊ loop in the left posterior and superior octant.

A difference in orientation between QRSsÊ loop patterns in children and adults has been reported by Grishman and Scherlis,[11] although these authors do not mention the progressive nature of this transition. The shift in orientation has also been described by Urschel and Abbey,[13] who suggest that elevated

diaphragms of persons within older age groups may be a contributing factor to the shift in orientation. Urschel and Abbey use mean spatial vectorcardiographic derivations from the electrocardiogram in their study.

It is suggested herein that in our series of cases a gradual transition exists, starting with the vector of right ventricular prominence present at birth, continuing through the normal range of orientation, and ending, finally, in the vector of left ventricular hypertrophy. This may be due to a gradual increase in the electromotive forces emanating from the left ventricle, especially from that portion of the left ventricle located near the base of the heart, as this anatomic area usually produces vector forces noted posteriorly and superiorly. On the basis of these observations, we suggest that shift of the QRSsÊ loop toward the posterior superior octant in a young individual may be an early change indicative of left ventricular hypertrophy. Determination of whether a significant shift to the posterior superior octant has occurred in an older individual is more difficult, as some shift toward that direction occurs normally. The possibility exists that some degree of left ventricular hypertrophy is a part of progressive age changes. Some of the vectors included by Grishman and Scherlis[11] in the group to which they refer as "questionably normal" exemplify excessive shift posteriorly and superiorly as compared with vectors in our series; these may represent early stages of left ventricular hypertrophy.

A QRSsÊ loop more anterior, inferior, and toward the right than is usual in an older person, on the other hand, may be an early clue to prominence of the right ventricle or loss of vector forces toward the left. Therefore, in interpreting the vectorcardiogram, the age of the subject must be kept constantly in mind.

In view of our finding that the direction of inscription of the frontal loop in normal adults may be either clockwise or counterclockwise (it is counterclockwise in all of our normal patients over the age of 80), we cannot accept the statement of Wolff and associates[14] that counterclockwise direction of the frontal loop is infrequent and is an indication of combined right and left ventricular hypertrophy.

The occurrence of many unexpected as well as heretofore anticipated vectorcardiographic variations in this series permits us to describe the normal pattern only in the generalities set forth in this paper under the heading "observations." The presence of these variations gives additional emphasis to the statement[14] that wide variations noted are due probably to the relatively small number of cases studied and the different reference systems used. This statement is true today and probably will remain true until many additional studies of normal persons have been made, with correlations drawn between normal and abnormal vectors, and autopsy studies made of these same hearts.

SUMMARY

1. One hundred presumably normal patients were studied by direct spatial vectorcardiographic methods using the modified cube technique.

2. The tracings were described in terms of relatively constant findings, as well as with commentary on unusual characteristics.

3. No correlation between direction of inscription of the frontal loop and the axis deviation or ECG-determined electrical position was noted, except in patients over 80 years of age.

4. By dividing the cases into decades by increasing ages, a trend in vector orientation from the anterior inferior toward the posterior superior octant was observed. In view of this transition with age, it is suggested that in the interpretation of vectorcardiograms the age of the patient be considered.

5. More specific criteria for the limitations of normal is indicated but necessitates collection of large series of normal cases and eventual pathologic correlation.

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SIGNIFICANCE OF THE RELATION OF QRS AND T WAVES IN BUNDLE BRANCH BLOCK: A USEFUL ELECTROCARDIOGRAPHIC SIGN

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BUNDLE branch block can be an innocuous incidental finding or a manifestation of cardiac disease. A large statistical study by White and associates[1] demonstrated a significant percentage of patients with right bundle branch block without clinical evidence of cardiac disease. In both left and right bundle branch block, evaluation of the status of the patient rests on clinical and electrocardiographic grounds, prognosis being most closely related to etiology of the heart disease and size of the heart.[1,2,3] In addition to these and other purely clinical criteria, cardiographic signs of value in deciding, in a given case, whether the conduction defect represents heart disease include the calculation of the ventricular gradient,[4,8] the study of the spatial QRSsÊ loop,[5] and the presence of Q waves.[6] The purpose of this paper is to point out an electrocardiographic sign in bundle branch block which indicates, in the majority of patients studied, the presence of severe organic heart disease.

The direction of the T wave in bundle branch block is generally opposite to that of the major QRS deflection,[7] the mean QRS vector,[4,8] or the QRSsÊ loop.[5] Hoffman and Schack pointed out that the spatial mean T vector in bundle branch block, when plotted on a cylindrical reference system of the Grant type,[4] generally makes a wide angle of 120 to 180 degrees in relation to the terminal or final 0.04 second of the QRS complex similarly plotted.[9]

This spatial angle, referred to as the F04-T angle, was narrow (110 degrees or less) in about 10 per cent of 130 cases of bundle branch block in their series. In all these patients severe organic heart disease was the basis for the conduction defect.

The present study of narrow F04-T angles in bundle branch block corroborates the clinical significance of this sign in 22 additional patients.

METHODS AND RESULTS

From the ECG files of the Long Island Jewish Hospital and Beth Israel Hospital, all records of the past 3 years which had been diagnosed as interventricular conduction disturbance or as bundle branch block were reviewed. In all records with QRS intervals of 0.12 second or greater, excluding those with short P-R interval, the spatial F04-T angle was determined. The vectors

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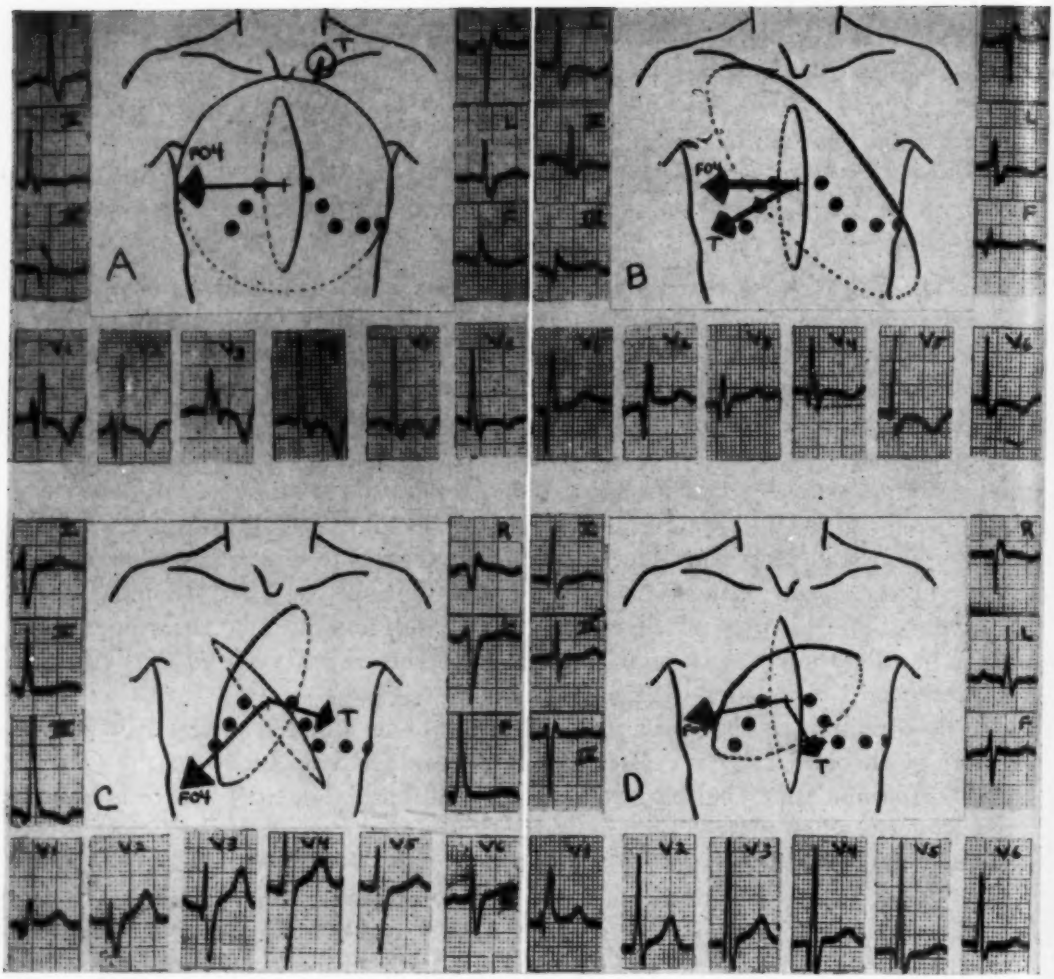


Fig. 1.—Electrocardiograms and diagram of F04-T angle in patients J. B. (*A*), E. T. (*B*), J. W. (*C*), and M. R. (*D*). Clinical data is presented in Table I.

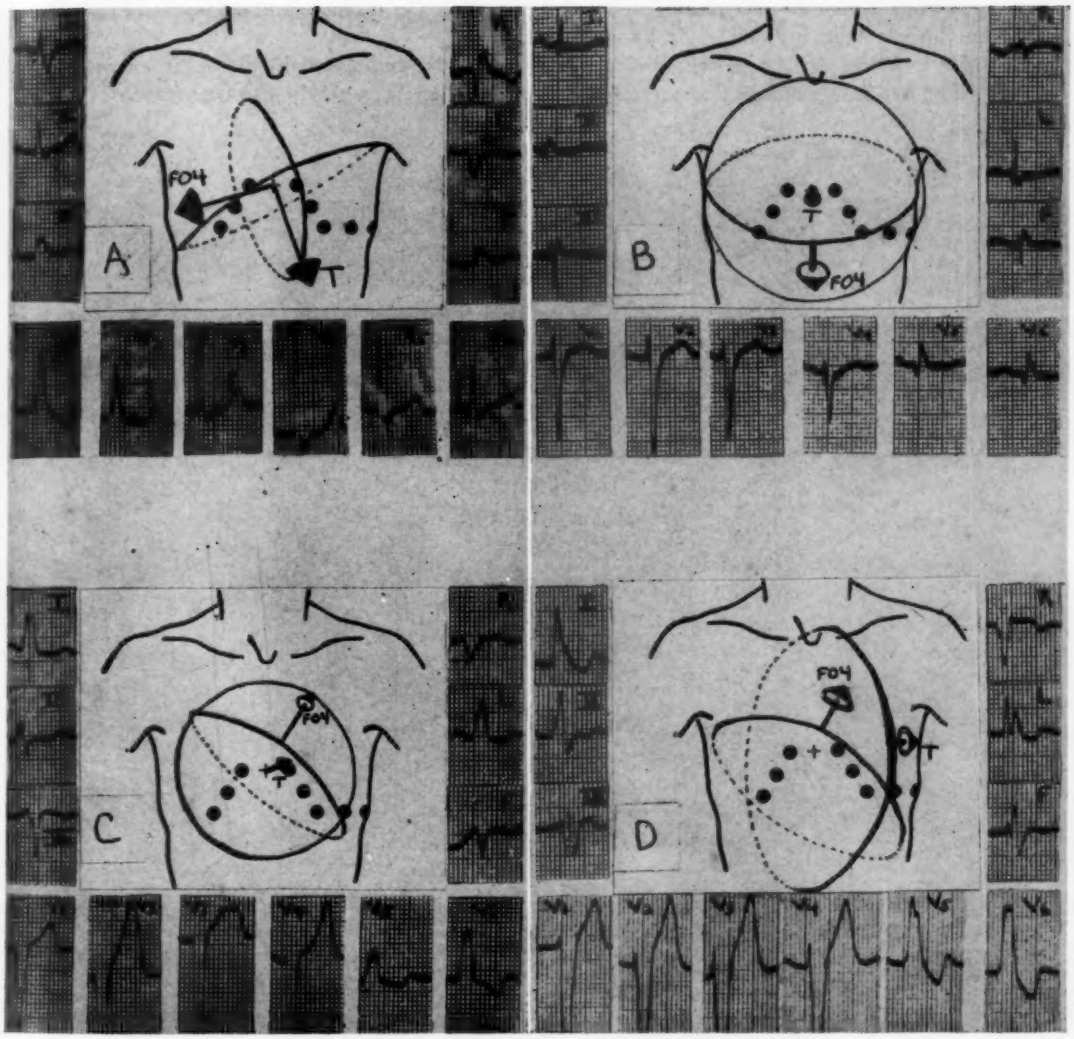


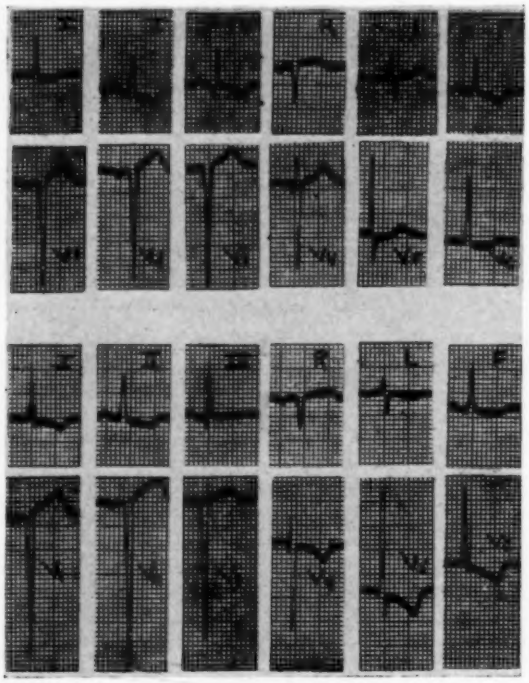
Fig. 2.—Electrocardiograms and diagram of F04-T angle in patients R. A. (*A*), D. W. (*B*), E. F. (*C*), and M. G. (*D*). Clinical data is presented in Table I.

were plotted on a model of the Grant cylinder, and the angle formed was measured with a protractor. Of 415 tracings analyzed, the F04-T angle was 100 degrees or less in 22 cases. The case histories were not known before the angles were measured, but were studied in detail subsequently.

In this series of 22 patients, all but 2 had unequivocal evidence of organic heart disease. The two exceptions were a 90-year-old man with right bundle branch block, and a 53-year-old woman with left bundle branch block.

Table I indicates the age, sex, clinical status, ECG diagnosis, and F04-T angle for each patient. The left-hand column shows the illustration number corresponding to each case.

A.



B.

Fig. 3.—Electrocardiograms of D. W. (52, M) with coronary artery disease. *A*, One week after admission. *B*, Two weeks after admission, after bouts of pain and paroxysmal nocturnal dyspnea. (Subsequent record showing BBB is seen in Fig. 4, *A*.)

DISCUSSION

Only a small percentage of bundle branch block tracings exhibit a narrow F04-T angle. Yet, in this group (22 of 415 cases, or 5 per cent) 20 patients had obvious organic heart disease, and 5 were dead at the time of writing. These facts, which agree with the results of Hoffman and Schack, indicate that the determination of the F04-T angle is of prognostic value in bundle branch block.

In right bundle branch block, which often occurs in the absence of heart disease, calculation of the ventricular gradient may be difficult because of the biphasic nature of the QRS complexes. In these cases, a narrow F04-T angle is strong evidence of disease and is against a benign etiology. Of our 16 instances of right bundle branch block, 15 had unequivocal heart disease. The exception was a 90-year-old man. Four of the 15 died within a few months after the tracing under study was taken.

An interesting confirmation of these results as they apply to right bundle branch block is to be found in the paper by Rosenbaum and Alvarez[10] on the myocarditis of Chagas' disease. In this disease right bundle branch block is frequent. The most severe, often fatal, cases had right bundle branch block with T_1 inverted. Indeed, this sign was recognized by the authors as helpful in deciding whether a given instance of right bundle branch block was trypanosomal in origin or not. Vector study, with our technique, of the published records

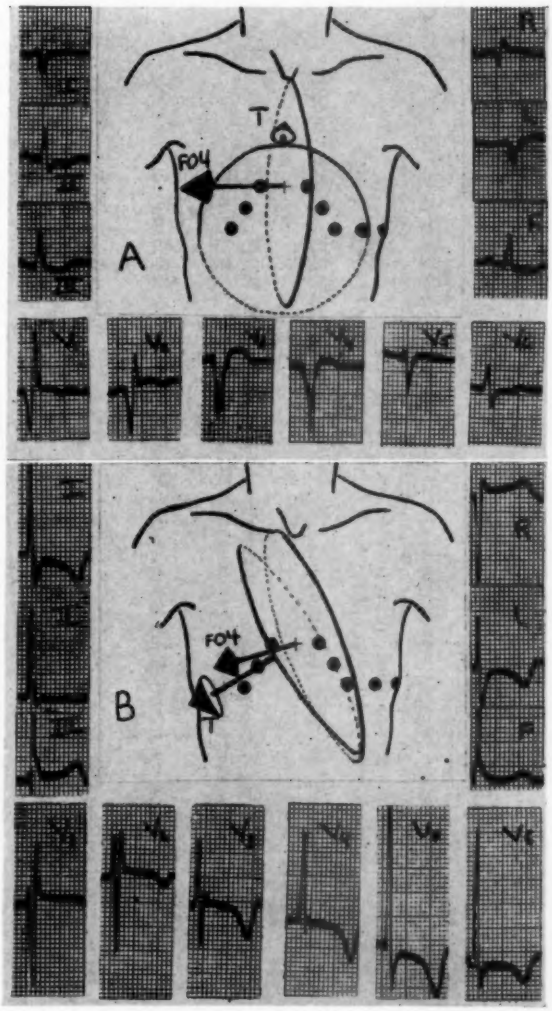


Fig. 4.—Electrocardiograms and diagram of F04-T angle in patients D. W. (*A*), and C. B. (*B*). Two previous records of D. W. are shown in Fig. 3.

of Rosenbaum and Alvarez in which inverted T_1 was manifest demonstrated F04-T angles of 30 to 100 degrees. It is necessary to emphasize strongly that although a narrow F04-T angle is indicative of organic heart disease, a wide angle by no means rules out this possibility.

TABLE I

ILLUSTRATION NUMBER	PATIENT	CLINICAL INFORMATION	ECG DIAGNOSIS	F04·T ANGLE (DEGREES)
1,*A*	J.B. 64 F	Hypertensive and arteriosclerotic heart disease, 6 yr.; angina decubitus and congestive failure	RBBB	95
1,*B*	E.T. 75 F	Hypertensive and arteriosclerotic heart disease; anginal syndrome, congestive failure; patient died of myocardial infarction 1 yr. after tracing was recorded	RBBB—septal infarction	30
1,*C*	J.W. 59 M	Arteriosclerotic heart disease; myocardial infarctions 7 and 5 yr. before admission; anginal syndrome; congestive failure; patient died of myocardial infarction 9 mo. after the tracing was recorded	RBBB—anteroseptal infarction	90
1,*D*	M.R. 90 M	No clinical evidence of heart disease	RBBB—1° A-V block	90
2,*A*	R.A. 41 M	Admitted for severe substernal oppression; clinical course and laboratory evidence indicative of acute myocardial infarction	RBBB	95
2,*B*	D.W. 45 M	Myocardial infarctions 6 and 4 yr. before admission; congestive failure 3 yr.	BBB, unspecified type	90
2,*C*	E.F. 67 M	Hypertensive heart disease of 15 yr. duration	LBBB	100
2,*D*	M.G. 47 F	Hypertensive heart disease; coronary insufficiency, 5 yr.; chronic congestive failure; patient died of coronary occlusion 1 yr. after tracing was recorded	LBBB	60
3,*A* 3,*B* 4,*A*	D.W. 52 M	Hypertensive and arteriosclerotic heart disease; persistent angina; acute left ventricular failure; acute myocardial infarction	(Fig. 3,*A*) Left ventricular hypertrophy (Fig. 3,*B*) Fresh myocardial damage (Fig. 4,*A*) RBBB—septal infarction	95
4,*B*	C.B. 61 F	Hypertensive heart disease; congestive failure of many years' duration	RBBB—2:1 A-V block	30

5,*A*	T.C. 59 M	Hypertension 8 yr. duration; myocardial infarction 3 yr. before admission	RBBB	80
5,*B*	N.D. 68 M	Arteriosclerotic heart disease; myocardial infarction 12 yr. before admission; chronic congestive heart failure	RBBB	90
5,*C*	H.H. 59 M	Hypertensive heart disease; chronic congestive failure; anginal syndrome; patient died the day after the tracing was recorded	RBBB	100
5,*D*	F.K. 53 F	No evidence of cardiac disease	LBBB	90
6,*A*	L.W. 73 M	Arteriosclerotic heart disease; myocardial infarction 3 mo. before admission	RBBB	30
6,B	J.A. 63 M	Hypertensive and arteriosclerotic heart disease; 2 previous myocardial infarctions; anginal syndrome	LBBB	60
6,*C*	N.M. 73 M	Arteriosclerotic heart disease; anginal syndrome, 7 yr. duration; bouts of coronary insufficiency	LBBB	75
6,*D*	H.G. 73 M	Arteriosclerotic heart disease; severe anginal syndrome	RBBB	20
7,*A*	R.R. 78 F	Aortic valvular stenosis; ventricular hypertrophy; congestive heart failure	RBBB	30
7,*B*	A.K. 75 F	Hypertensive and arteriosclerotic heart disease; myocardial infarction 6 yr. before admission; admitted for fresh myocardial infarction	RBBB	70
7,*C*	O.E. 78 M	Hypertensive and arteriosclerotic heart disease; chronic congestive heart failure	LBBB	60
7,D	Z.F. 66 M	Patient admitted for mild chest pain; work-up negative; patient expired 2 mo. later of myocardial infarction	LBBB	90

The problem of left bundle branch block deserves brief special comment. Generally speaking, this conduction defect is a manifestation of organic disease. Therefore, estimation of the F04-T angle is of less value. In addition, determination of the ventricular gradient is easier in left than in right bundle branch block. Furthermore, of the 5 instances of left bundle branch block in the present study, 1 was the record of a 53-year-old woman with no evidence of heart disease. For these several reasons the determination of F04-T angles must be considered of greatest value in right bundle branch block.

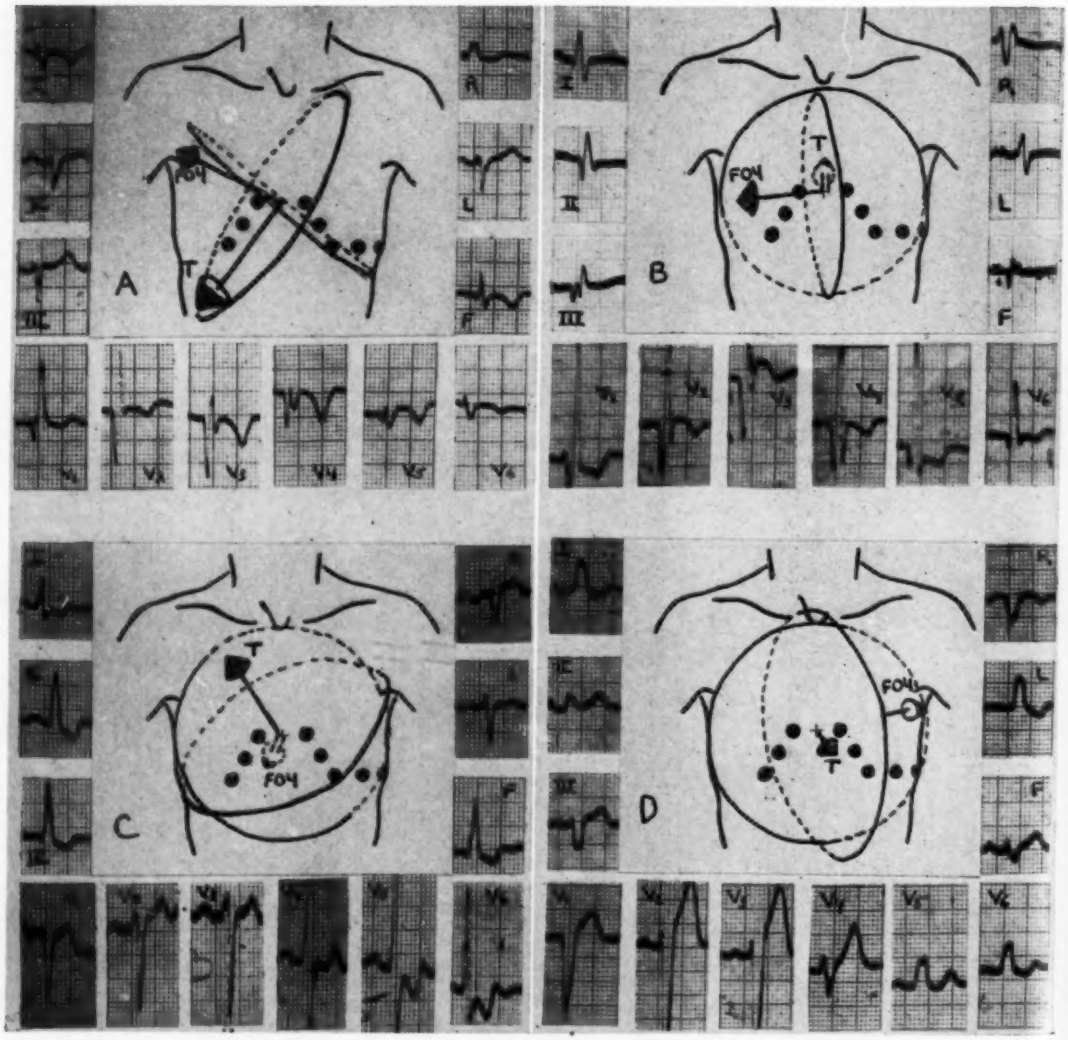


Fig. 5.—Electrocardiograms and diagram of F04-T angle in patients T. C. (*A*), N. D. (*B*), H. H. (*C*), and F. K. (*D*).

SUMMARY AND CONCLUSIONS

1. The spatial angle formed by the terminal 0.04 second of QRS and the mean T vector (F04-T angle) was 100 degrees or less in 22 of 415 instances of bundle branch block. Of these, 16 were right, and 5 left, bundle branch block. One was of indeterminate type.

2. Twenty of the 22 patients had obvious severe cardiac disease, and 5 died of their disease.

3. Determination of the F04-T angle may prove to be a valuable diagnostic sign, especially in the evaluation of right bundle branch block.

The authors wish to thank Mrs. Mary Berman for valuable technical assistance.

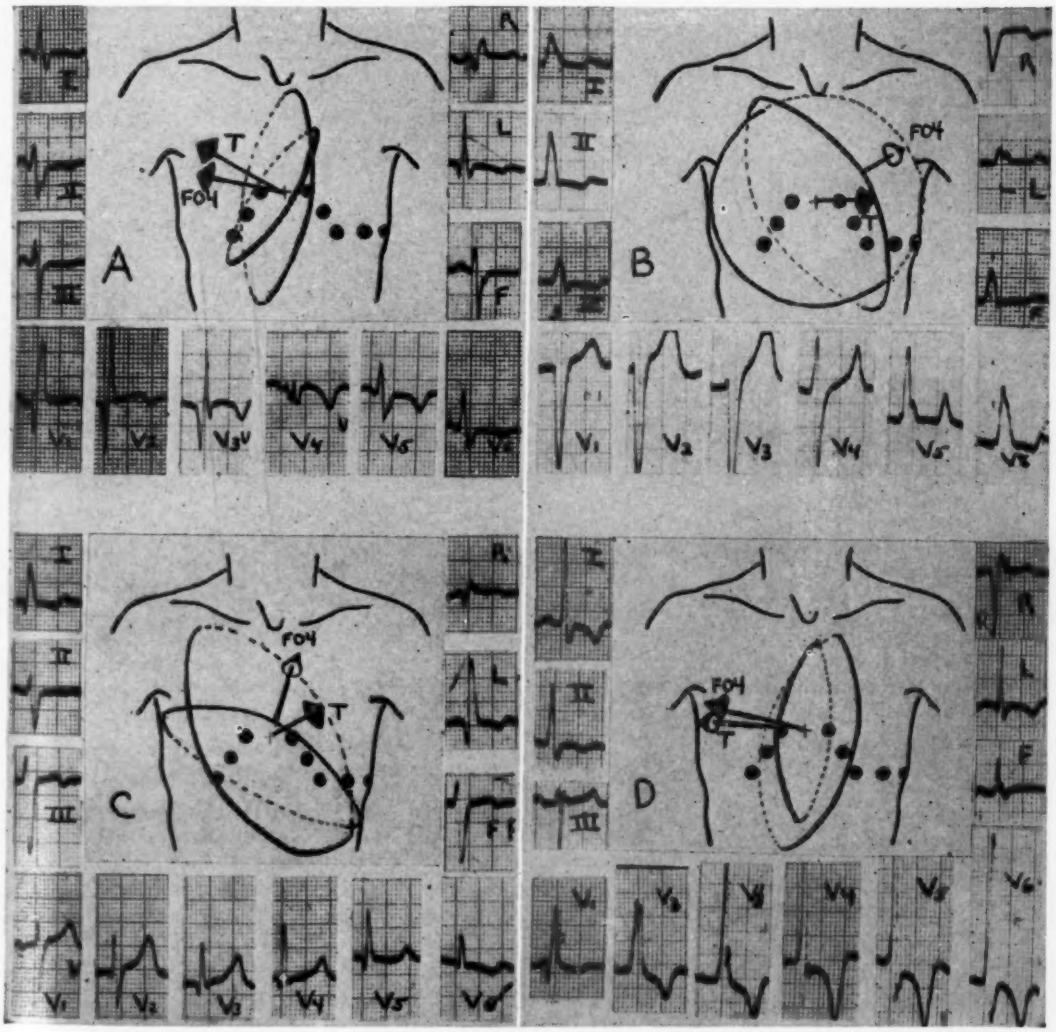


Fig. 6.—Electrocardiograms and diagram of F04-T angle in patients L. W. (*A*), J. A. (*B*), N. M. (*C*), and H. G. (*D*).

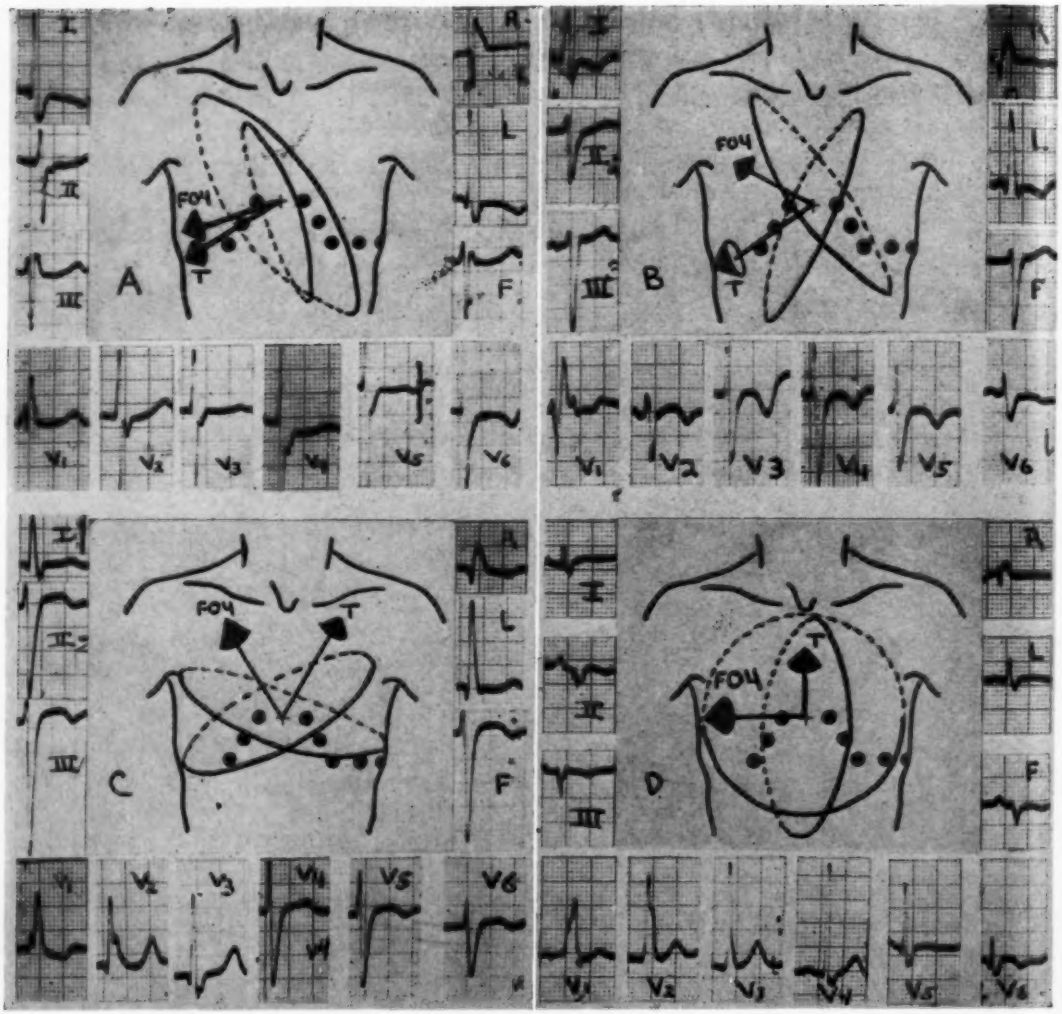


Fig. 7.—Electrocardiograms and diagram of F04-T angle in patients R. R. (*A*), A. K. (*B*), O. E. (C), and Z. F. (*D*).

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Clinical Reports

SIMULTANEOUS ATRIAL AND NODAL TACHYCARDIA

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INTRODUCTION

THE simultaneous occurrence of atrial and nodal tachycardia has been reported very infrequently. Three of the 4 previously published cases were thought to be due to digitalis intoxication, while no clinical description is available in the remaining one.[1-4] In recent years, the development of atrial arrhythmias secondary to excessive digitalis therapy has received renewed emphasis, and the efficacy of potassium administration in the treatment of atrial tachycardia with block has been established.[5] It is the purpose of this paper to report a case of simultaneous atrial tachycardia and nodal tachycardia probably due to digitalis intoxication, with recovery following the administration of intravenous potassium chloride.

CASE REPORT

B. F., a 69-year-old white woman, was admitted to the Jewish Hospital for the twelfth time on Sept. 26, 1955, with a history of rheumatoid arthritis of 5 years' duration, during which time she had been treated with cortisone, intramuscular ACTH, and prednisone. Shortly prior to admission, the steroid therapy was discontinued, following which a severe recrudescence of her arthritis occurred. In 1941, she first experienced recurrent palpitation and syncope, the exact etiology of which was not determined. Occasional bouts of palpitation continued to occur despite maintenance treatment with quinidine. In 1951, an episode of nodal tachycardia occurred, confirmed by electrocardiogram. Ambulatory quinidine therapy was again instituted, and maintained to the present admission. In 1954, because of a recurrence of the arrhythmia, she was slowly digitalized and maintained on Digilanid, 0.33 mg. per day.

On admission to the hospital, her blood pressure was 140/60 mm. Hg, pulse 84 and regular. She was acutely ill and moderately dyspneic. Examination of the chest revealed moderate kyphoscoliosis, and the lungs were clear. There was a Grade 3, low-pitched, blowing, systolic murmur over the entire precordium, heard for the first time, on this admission. Examination of the hands revealed typical deformities of rheumatoid arthritis. Chest x-ray showed a small, left pleural effusion which could not be aspirated. She was again placed on heavy doses of ACTH, cortisone, and potassium supplements and responded well. Initially, she received ACTH gel, 25 units intramuscularly daily for one week, followed by cortisone, 100 mg. three times daily. The

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cortisone was reduced to 50 mg. daily over a 3 week period. The dosage was then intermittently increased, and ACTH gel, 25 units intramuscularly daily, was added on Oct. 27, 1955. She continued to receive quinidine, 0.2 Gm. 3 times daily, and Digilanid, 0.33 mg. daily. Subsequently, "L.E." cells were seen on four peripheral blood preparations, and a diagnosis of lupus erythematosis was made.

Laboratory results revealed normal urinalysis and blood counts. Blood urea nitrogen was 9 mg. per 100 c.c., fasting blood sugar 67 mg. per 100 c.c., serum sodium 138 meq. per liter, serum potassium 4.7 meq. per liter, and serum chlorides 100 meq. per liter.

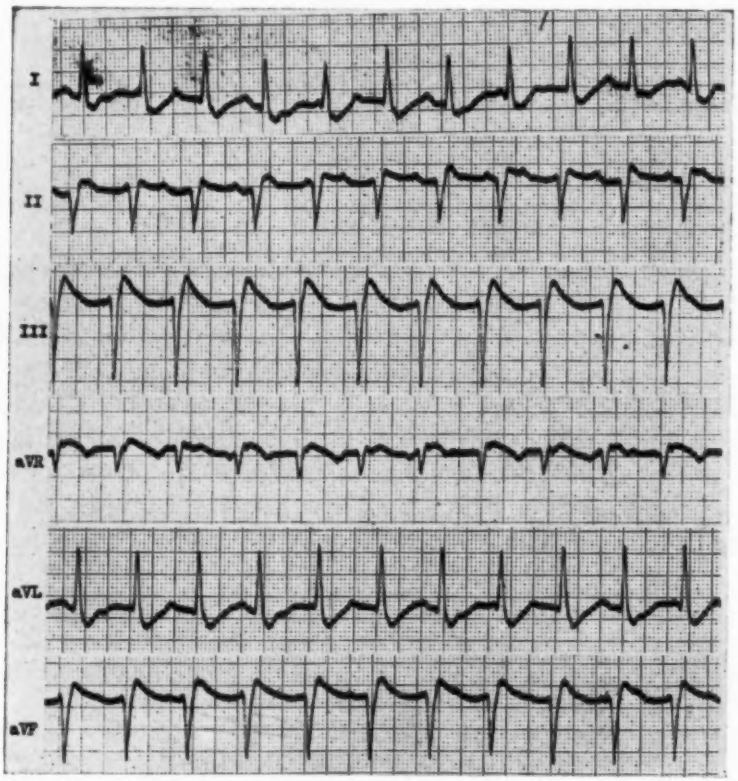

Fig. 1.—Electrocardiogram taken on Dec. 14, 1955, shortly after the onset of shock. The P waves and QRS complexes are regular. Atrial and nodal tachycardias are simultaneously present.

On Nov. 11, 1955, the patient suddenly developed severe chest pain accompanied by shock. Electrocardiogram at that time revealed acute lateral and diaphragmatic wall infarction, sinus bradycardia of 46 with runs of atrial fibrillation. There were a few ventricular premature contractions, and the P-R interval was 0.16. The potassium chloride therapy was then discontinued, although the digitalis, quinidine, and steroid therapy was continued.

The patient began to convalesce from her myocardial infarction uneventfully except for a regular pulse of 100, which she developed on Dec. 10, 1955. On December 14, at 1:45 P.M., she became severely dyspneic and appeared to be in shock. Several injections of Wyamine failed to elevate the blood pressure. The electrocardiogram revealed a simultaneous atrial and nodal tachycardia (Fig. 1). The atrial rate was 185 and the ventricular rate was 110. There was no apparent relationship between the P waves and the QRS complexes. Because of the suspicion that digitalis intoxication may have been present, an infusion was begun at 7:00 P.M., containing 40 meq. of potassium chloride in 500 c.c. of 5 per cent dextrose in water. At 7:30 P.M., approximately 165 c.c. of the infusion was administered and the auricular rate slowed to 160. The ventricular rate was 108. At 7:55 P.M., the auricular rate slowed to 140 while the ventricular rate

remained 110. At 8:20 P.M., 80 minutes after the infusion was begun, the ventricular rate was 105 and regular, and there were slow, irregular multiform P waves present with occasional ventricular premature contractions. Concomitant with the disappearance of the atrial tachycardia, the patient abruptly came out of shock and her clinical appearance markedly improved. (The reasons for this improvement are somewhat obscure since the ventricular rate remained essentially unchanged.) A 9:00 P.M., there was a slightly irregular ventricular rate of 98, the auricular rate being 64 and regular. On December 15, the following day, 40 meq. of potassium chloride in 500 c.c. of 5 per cent dextrose in water was given and Pronestyl 500 mg. intramuscularly every 6 hours was begun. That afternoon, the auricular rate was 53 and the ventricular rate was 85 with A-V dissociation and frequent interference beats. Serum sodium was 143 meq. per liter, serum potassium 3.2 meq. per liter, serum chlorides, 101 meq. per liter, and the blood urea nitrogen was 10 mg. per 100 c.c.

On December 16, nodal tachycardia was present with 2:1 retrograde block, with a ventricular rate of 105 (Fig. 2). Serum sodium was 135 meq. per liter, and serum potassium 4.2 meq. per liter.

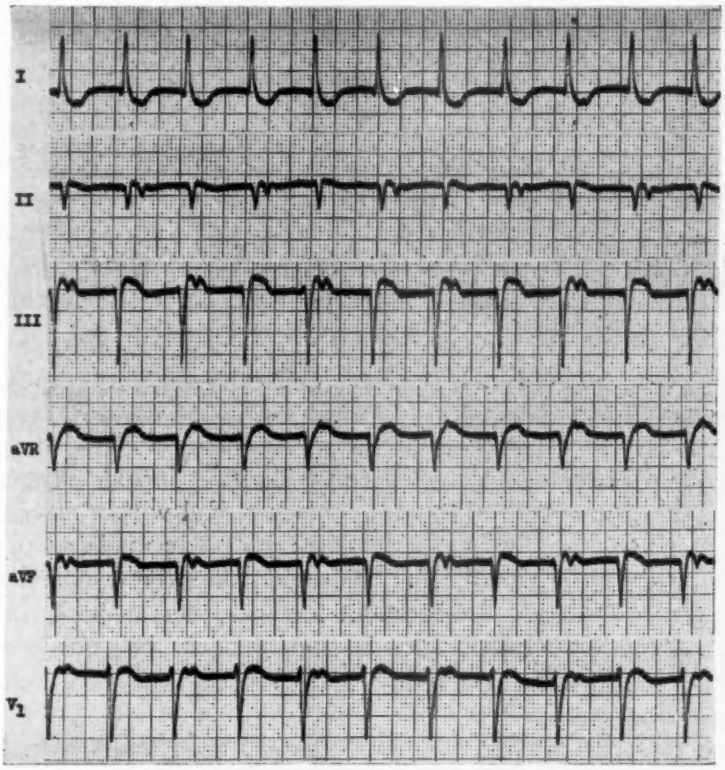

Fig. 2.—Electrocardiogram taken on Dec. 16, 1955. Nodal tachycardia with 2:1 retrograde block is present.

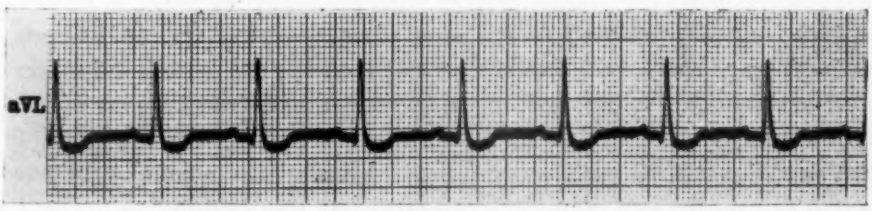

Fig. 3.—Electrocardiogram taken on Dec. 17, 1955. Sinus rhythm is now present.

The next day the electrocardiogram revealed a sinus rhythm with a rate of 85 and P-R interval of 0.18 seconds (Fig. 3). Serum electrolytes remained normal and the patient's clinical course continued uneventfully. The sinus rhythm persisted until discharge from the hospital on Jan. 26, 1956.

DISCUSSION

The initial electrocardiogram taken at the onset of shock showed regular P waves with a rate of 185 and regular QRS complexes, supraventricular in form, with a rate of 110. Since there was no apparent association between P waves and QRS complexes, it was felt that two independent, simultaneous stimulatory foci were present. Although the occurrence of either atrial or nodal ectopic rhythms is well recognized as a manifestation of digitalis intoxication,[6,7] the simultaneous occurrence of atrial and nodal tachycardia is very rare according to published reports.

TABLE I. PREVIOUSLY REPORTED CASES OF SIMULTANEOUS ATRIAL AND NODAL TACHYCARDIA

YEAR	NAME	ATRIAL RATE	NODAL RATE	PROBABLE DIGITALIS INTOXICATION	SURVIVED
1925	Luten*	170	92	Yes	No
1927	Howard	195	160	Yes	No
1952	Bernstein	190	118	Yes	No
1956	Katz and Pick	200	115	?	?

*In addition, 2 other cases in Luten's report may have had simultaneous atrial and nodal tachycardia, but this cannot be established with certainty from the available information.

In 3 of the 4 previously reported cases, digitalis intoxication has been incriminated as the cause, and all of these patients died within a very short time (Table I). In Katz and Pick's case no statement was made as to the clinical course of the patient. It would seem, therefore, that the occurrence of this arrhythmia is a very ominous development and is either an indication of severe heart disease or marked digitalis intoxication or both. To our knowledge this is the first instance in which potassium was used therapeutically and in which recovery occurred.

Although this patient had previously experienced bouts of palpitation including one verified episode of nodal tachycardia, we believe that digitalis intoxication probably was responsbile for inducing the arrhythmia in this instance. The toxic effects of digitalis are much more prominent in patients who have severe underlying heart disease.[8] This elderly lady had had an acute myocardial infarction just four and one-half weeks prior to the onset of the arrhythmia. She had received large doses of adrenal cortical steroids for an extended period of time, and supplementary potassium replacement had been discontinued. The danger of digitalis intoxication in patients receiving steroids due to increased excretion of potassium is well recognized.[9] Finally, the cessation of the atrial tachycardia during the intravenous administration of potassium chloride strongly suggests that at least the ectopic atrial rhythm was secondary to digitalis intoxi-

cation. It is interesting to note that before the atrial tachycardia was reverted, the atrial rate per se did slow during the infusion similar to those cases of atrial tachycardia with block due to digitalis intoxication reported by Lown and Levine.[10]

Because of the suspicion that digitalis intoxication may have been present, potassium chloride therapy was instituted. Although the efficacy of potassium administration in the treatment of digitalis-induced arrhythmias is well established, the mechanism of action is not yet clear. According to Szent-Gyorgyi,[11] a medium of potassium ions within the myocardial cell inhibits the contraction of myosin, an intracellular myocardial protein. When depolarization occurs, the potassium ions pass across the cell membrane, and their inhibition of the intracellular contractile proteins is released. Digitalis may in some way change or influence either the contractile elements or the intracellular concentration of potassium. Toxic doses of digitalis are said to liberate potassium from the myocardial cell.[12] In any case it appears that potassium inhibits the development of digitalis toxicity, both on isolated muscle preparations in vitro and in clinical studies in man.[13,14] As suggested by Friedman and associates,[15] however, the antagonistic actions of digitalis and potassium may be due to the depressant effect alone of potassium on irritability. Until the metabolic alterations which occur in congestive failure and their relationship to both digitalis and potassium are more clearly understood, one must be cautious in interpreting the exact mechanisms involved.

SUMMARY

A case of simultaneous atrial and nodal tachycardia, probably due to digitalis intoxication, is reported. Recovery occurred following the intravenous infusion of potassium chloride. The evolution of the atrial rhythm was similar to that which occurs in digitalis-induced atrial tachycardia with block. Although potassium administration has proved to be valuable in the treatment of arrhythmias due to digitalis toxicity, the mechanisms involved remain obscure.

We wish to thank Dr. Llewellyn Sale, Sr., for permitting us to study and present this case, and Dr. Edward Massie for his valuable aid in the preparation of this manuscript.

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PARTIAL ANOMALOUS VENOUS CONNECTION

A Case Report Illustrating Diagnostic Techniques

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ABERRANT pulmonary venous connection, once a pathologic curiosity, is now of practical clinical interest. This interest reflects the development of techniques which permit accurate ante-mortem diagnosis and the susceptibility of these anomalies to surgical correction. The diagnosis may be suspected on a routine cardiovascular evaluation, but angiocardiography and cardiac catheterization are necessary to confirm the presence and determine the extent of the anomaly. Differentiation between partial anomalous pulmonary venous connection and interatrial septal defect, or the recognition of their coexistence, may be difficult. Both are forms of aberrant pulmonary venous drainage.[1]

We recently studied a patient with an interatrial septal defect in whom a right pulmonary vein entered the inferior vena cava. The clinical findings and diagnostic techniques employed are presented.

CASE REPORT

The patient, aged 26 years, came to the United States from Ireland in 1953. Four months after entering the U. S. Army he was hospitalized with the chief complaint of abdominal distress subsequently shown to reflect a duodenal ulcer. He was transferred to Walter Reed Army Hospital with the tentative diagnosis of anomalous pulmonary venous connection when a routine chest x-ray revealed cardiomegaly associated with an abnormal vascular shadow. Since adolescence he had had occasional palpitation and infrequent transient chest pain of a pleuritic quality. He was first told that he had an enlarged heart after a routine chest x-ray 6 years before admission. Two years prior to admission a clinical diagnosis of interatrial septal defect was made. The patient's first recognition of a relative decrease in exercise tolerance came during his basic training when his performance rating in physical training tests fell well below average. Only by comparison with his associates was he aware of any physical limitation. At no time had cyanosis been recognized.

Physical examination revealed a normally developed, acyanotic, healthy appearing male. His arm blood pressure was 120/65 and his leg blood pressure, 130/72 mm. Hg. Slight prominence of the left side of the chest, relative prominence with splitting of the second sound in the pulmonic area, and a Grade 2 blowing systolic murmur maximal in the second left intercostal space were the only abnormal findings.

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Routine laboratory studies, including hematocrit, were normal. An electrocardiogram revealed sinus rhythm and right axis deviation. The QRS duration was 0.10 second. In V_1 the intrinsicoid deflection was delayed. Lead aV_R manifested a prominent terminal R wave. Prominent S waves persisted in the precordial leads through V_6 (Fig. 1). These findings were felt to be compatible with right ventricular predominance of the so-called diastolic overload type.[2] Posteroanterior and lateral roentgenograms of the chest revealed enlargement of the right side of the heart associated with a prominent pulmonary artery and increased pulmonary vascular markings. There was an abnormal vascular shadow extending along the right cardiac border which was thought to be characteristic of an anomalous pulmonary vein (Fig. 2). Angiocardiography performed with 50 c.c. of 70 per cent iodopyracet (Diodrast) injected through the left cephalic vein revealed enlargement of the right side of the heart and prominence of the central

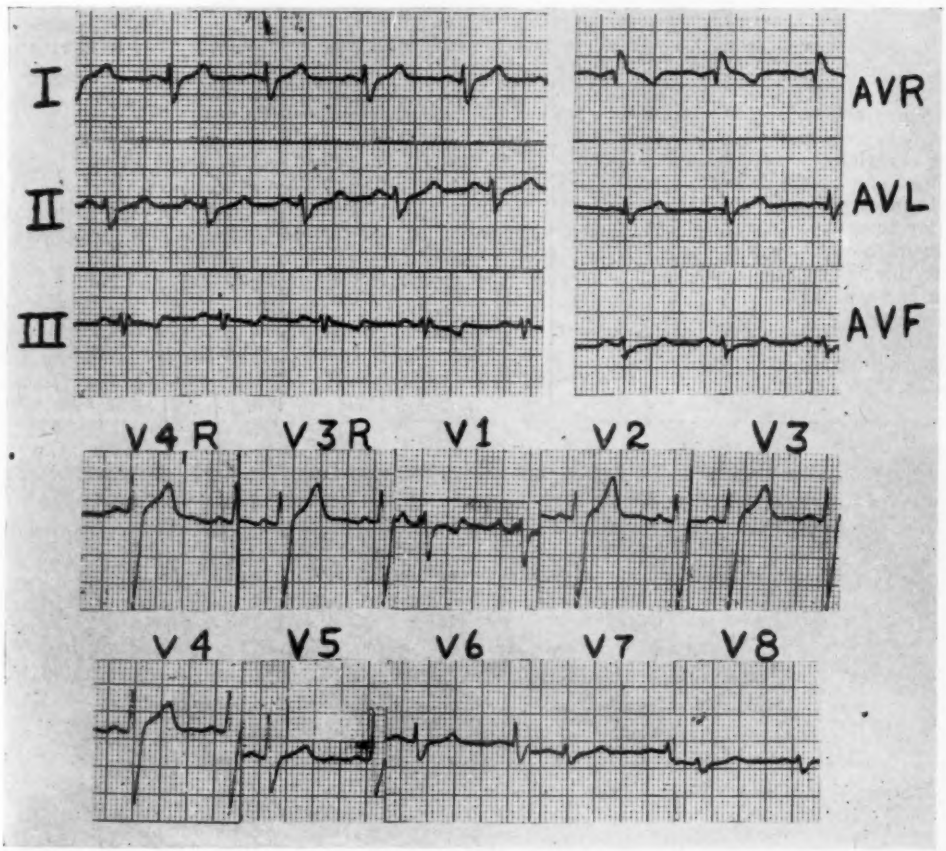


Fig. 1.—Electrocardiogram of the patient on March 20, 1956, including the standard limb leads and precordial leads from V_4R through V_8. Normal sinus rhythm. P-R interval 0.17 second. QRS interval 0.10 second. There is right axis deviation with a 0.05 second delay in the intrinsicoid deflection in V_1. A deep S wave is noted in all the precordial leads through V_8. These findings were interpreted as being consistent with right ventricular predominance of the so-called diastolic overload type.[2]

pulmonary arteries. An anomalous pulmonary artery arose from the major branch to the right lower lobe and descended adjacent to the spine toward the diaphragm. The right juxtacardiac vascular shadow noted in the plain x-ray films filled coincidentally with the left pulmonary veins. It connected superiorly with several prominent vessels extending down vertically from the right upper lobe. The vessel widened appreciably as it descended and disappeared behind the diaphragm at the right cardiophrenic angle. No right pulmonary veins were visualized entering

the left atrium (Fig. 3). Persistent opacification of the right side of the heart and pulmonary vessels suggested recirculation through the lungs and the right side of the heart.

Catheterization of the right side of the heart was performed through the left median basilic vein. Pressures were measured with a Statham P23D pressure transducer connected to a four-channel Sanborn Poly-Viso direct-writing recording system. The Beckman spectrophotometer was employed for measuring blood oxygen saturations. The findings, listed in Table I, were those of a left-to-right shunt at the atrial level and were consistent with aberrant pulmonary venous drainage. Repeated probing was attempted during the procedure, but neither an aberrant vein nor an interatrial defect was entered.

TABLE I. CARDIAC CATHETERIZATION RESULTS

LOCATION	PRESSURE (MM. Hg)	BLOOD OXYGEN (PER CENT SATURATION)
Pulmonary artery	27/10	83.4
Pulmonary capillary	10/2	
Right ventricle	27/0–5	83.0
Inferior vena cava (T12-L1)		75.5
Inferior vena cava (T-11)		73.3
Inferior vena cava (near mouth)		72.3
Upper third right atrium	8/0	85.0
Lower third right atrium		87.4
Superior vena cava		57.5
Femoral artery		97.0
Estimated left-to-right shunt was approximately 50 per cent of pulmonary artery flow		

Because an interatrial septal defect commonly accompanies anomalous pulmonary veins, catheterization through the saphenous vein was felt advisable. An atrial defect may be traversed more readily from this approach. Regional angiocardiography in the pulmonary artery or anomalous vein, if entered, was planned to delineate more clearly the site of the emptying of the pulmonary vein.[3,4]

A Cournand needle was inserted into the left femoral artery and a double lumen cardiac catheter was passed via the right saphenous vein. The catheter was positioned with one opening in the inferior vena cava and the other in the mid-portion of the right atrium. Blood samples were collected simultaneously from these sites and from the femoral artery. The catheter was then positioned with one opening in the superior vena cava and the other in the atrium and simultaneous samples were again collected. The oxygen contents of these samples (Van Slyke manometric method) are listed in Table II.

TABLE II. SIMULTANEOUS BLOOD SAMPLES OBTAINED FROM SPECIFIED LOCATIONS AT TIME OF CARDIAC CATHETERIZATION

LOCATION	BLOOD OXYGEN (PER CENT SATURATION)
Inferior vena cava	79.2
Right atrium	86.8
Femoral artery	97.3
Superior vena cava	64.4
Right atrium	80.6
Femoral artery	96.9

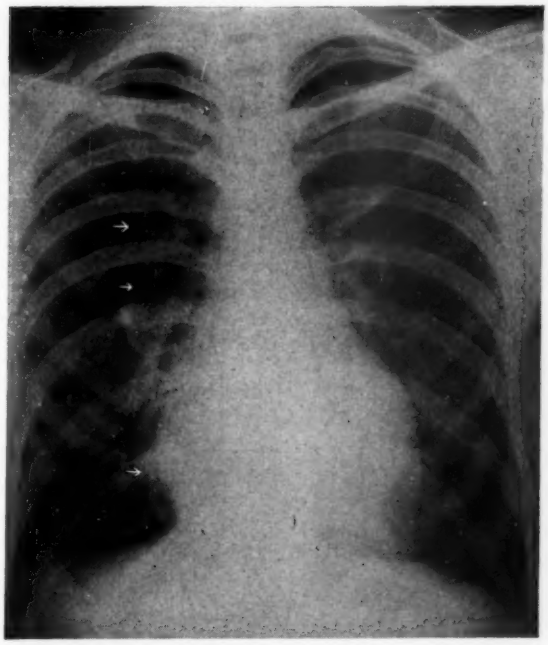
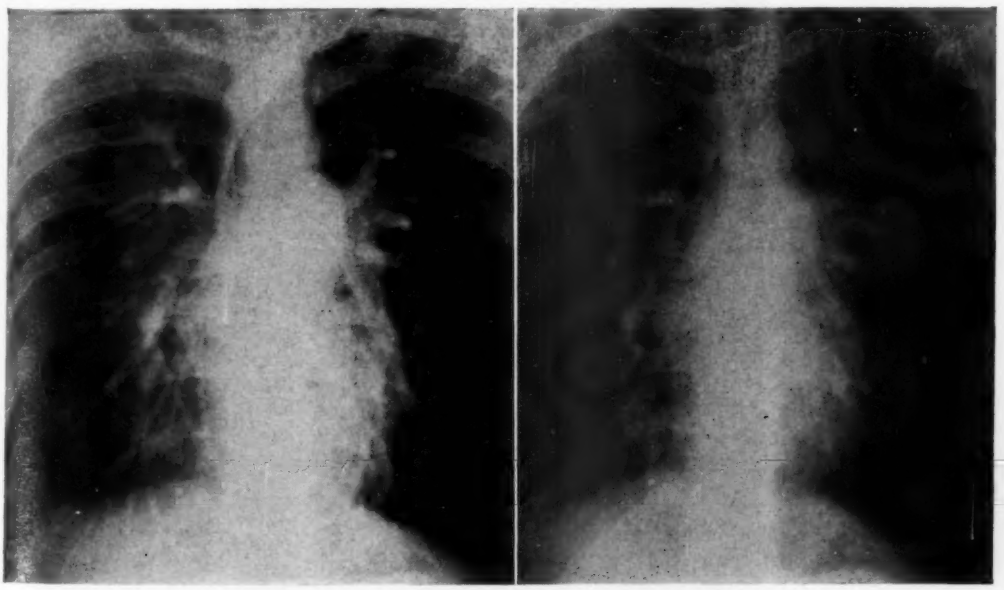


Fig. 2.—Posteroanterior roentgenogram of the chest. Arrows identify the abnormal right juxtacardiac shadow which was demonstrated to be an anomalous right pulmonary vein. There is evidence of right-sided enlargement associated with a prominent pulmonary artery and increased pulmonary vascular markings.



A. *B.*

Fig. 3.—Angiocardiogram performed with 50 ml. of 70 per cent Diodrast. *A*, Posteroanterior film 3 seconds after injection into the left median basilic vein revealed prominence of the right cardiac silhouette and central pulmonary arteries. An anomalous right pulmonary artery arising from the major branch to the lower lobe descends adjacent to the vertebral silhouette. *B*, Posteroanterior film 7½ seconds after injection revealing opacification of the right juxtacardiac shadow (arrows) seen in Fig. 2. Simultaneous opacification of the left pulmonary veins is demonstrated. The vessel receives tributaries from the right upper lobe. Enlarging as it descends, it disappears behind the diaphragm at the right cardiophrenic angle.

A catheter with an inflatable balloon at its tip was then passed. It entered the left atrium by traversing an interatrial septal defect. With the catheter in the left atrium, the balloon was inflated with 4 c.c. of sodium acetrizoate (Urokon) and withdrawn until it engaged the septum. The balloon was deflated until it just could be withdrawn through the defect. At this time, the balloon was 13 mm. in diameter. This was considered to represent the smallest diameter of the defect.

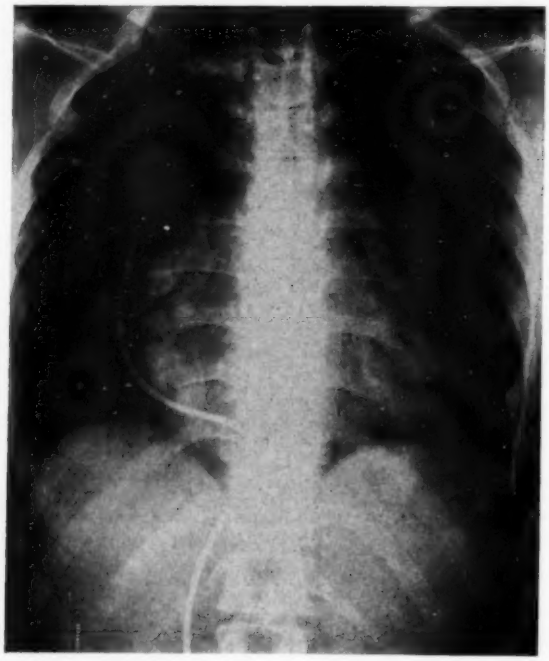


Fig. 4.—Posteroanterior roentgenogram revealing a Lehman catheter entering the right upper lobe through an anomalous pulmonary vein. (Armed Forces Institute of Pathology, No. 56-4666.)

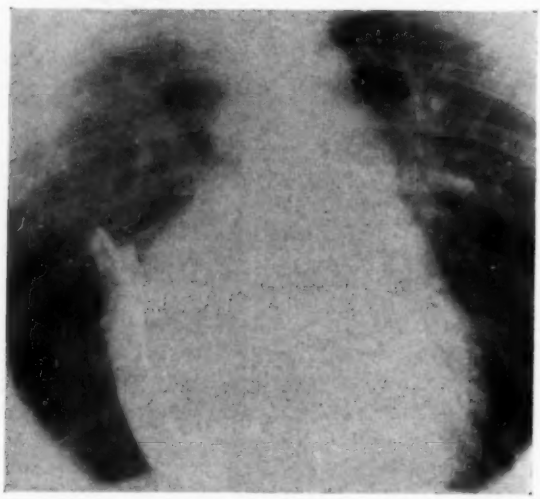


Fig. 5.—Anteroposterior view of the chest after the injection of 12 ml. of 70 per cent Urokon through a Lehman catheter in the right anomalous pulmonary vein. (Armed Forces Institute of Pathology, No. 56-4667.)

After withdrawal of the balloon catheter, a Lehman catheter was inserted to the junction of the right atrium and the inferior vena cava. It readily entered an anomalous vein and passed to the right upper lobe (Fig. 4). Two other pulmonary veins were entered from the right cardiac border. It was impossible to determine whether these were branches of the main paracardiac vein or whether they connected separately. The catheter tip was withdrawn to a position near the opening of the vein seen in Fig. 4. Twelve cubic centimeters of 70 per cent sodium acetrizoate (Urokon) were injected and biplane roentgenograms, at 4 per second, were obtained. One of the films is reproduced in Fig. 5.

DISCUSSION

Clinical, radiographic, angiocardiographic, and cardiac catheterization findings suggesting anomalous pulmonary venous connection have been described previously.[4-12] The picture varies according to the extent of the aberrant connection.[13] When all the pulmonary veins connect with the right side of the heart or the venous circulation, an associated defect permitting a shunt from the right to the left side of the heart is required for survival. This most frequently takes the form of a patent foramen ovale or interatrial septal defect.[1,13] Arterial unsaturation is invariably present. When the anomalous connection drains only a portion of the pulmonary circulation, an associated interatrial defect is commonly present.[9] As the hemodynamic alterations and resultant clinical cardiovascular changes associated with partial aberrant venous connection approximate those of an interatrial septal defect, the differential diagnosis may be difficult in the absence of clear roentgen delineation of a vascular anomaly. It is more difficult to determine the presence or absence of an atrial septal defect associated with a recognized anomalous pulmonary vein. Routine venous angiography usually fails to supply the answer unless a significant right-to-left shunt at the atrial level exists. The problem may not be resolved by catheterization unless the defect is traversed by the catheter. Conversely, in the presence of an interatrial septal defect, an incorrect impression that an anomalous vein exists may be gained when the catheter appears to pass from the right atrium directly into the lung field.[14] This may be clarified by observation in the oblique or lateral view which will show the catheter passing posteriorly into the left atrium before entering the right lung field. The use of dye dilution curves in association with catheterization may aid in resolving this problem.[9] The determination of nitrous oxide levels in the right side of the heart also may be of value in localizing a left-to-right shunt.[15]

In our patient, the question of an associated septal defect was left unsettled by the initial catheterization and angiocardiographic studies. Also, the exact point of entrance of the right pulmonary veins was uncertain. Recognizing the relative ease of traversing an interatrial septal defect from the inferior vena cava, a second catheterization was performed through the saphenous vein. Both the left atrium and the anomalous vein were entered. The anomalous pulmonary venous connection with the inferior vena cava adjacent to the right atrium was verified further by regional venography.

In approaching the patient's problem therapeutically, it was not deemed advisable merely to reduce the circulatory load on the right side of the heart by ligation of the right pulmonary artery.[4] The safety factor provided by a lung with anomalous venous connection in the event of injury to the opposite lung

has been considered by others.[4,5,11] In some instances, an anomalous pulmonary vein may be transferred directly to the left atrium.[16] Several methods are currently available for repair of an interatrial septal defect.[17-20] However, for the problems that might arise in attempting full correction of the aberrant pulmonary venous drainage in this situation, it was thought that a mechanical heart-lung preparation would be desirable. It was our opinion that the risk involved was not warranted at this time in view of the patient's minimal disability.

SUMMARY

A case in which the right pulmonary circulation drained into the inferior vena cava adjacent to the right atrium is presented. Intravenous angiocardiography demonstrated the anomalous venous pattern. Cardiac catheterization through the basilic vein revealed a left-to-right shunt at the atrial level. Catheterization through the saphenous vein demonstrated an interatrial septal defect and permitted passage of the catheter into the aberrant vein where regional venography was performed. The problem of differentiating partial aberrant pulmonary venous connection from an interatrial septal defect and, more particularly, of diagnosing interatrial defect in the presence of an anomalous vein is discussed.

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ANOMALOUS LEFT CORONARY ARTERY

Adult Type

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THE length and the distribution of the human coronary arteries may vary from heart to heart. The point of origin of the coronary arteries, on the other hand, deviates from the usual anatomic pattern only infrequently. Here an anomaly may exist in (a) the number, the size, or the location of the ostia by which the coronary vessels get their blood from the aorta, (b) the ostia being located in the branches of the aorta instead of in their usual location in the aorta proper, (c) the ostia being located in the pulmonary artery. These anomalies in the point of origin of the coronary arteries are of no clinical significance as long as all parts of the myocardium are adequately supplied by oxygenated blood. When the coronary arteries originate in the pulmonary artery, unoxygenated blood is delivered to the myocardium under reduced pressure. Such anomaly usually leads to degenerative changes in the heart and becomes manifested clinically as the Bland-White-Garland syndrome in the first few months of the extrauterine life. These infants seldom live to be one year of age. Review of the medical literature reveals that 48 cases of the infant type of anomalous left coronary artery have been reported.[3,5,9,10,13]

Occasionally, an individual with anomalous left coronary artery lives out a normal life span, symptom free. The medical literature contains reports of 11 adult and teen-age individuals with anomalous left coronary artery originating in the pulmonary artery.[1,4,6,8,11,12,14-17] To these we wish to add the case of an 18-year-old boy.

CASE REPORT

History.—Z. S., an 18-year-old Negro, always considered himself in good health. He never had exertional dyspnea, cyanosis, orthopnea, or palpitation. He had never restricted his activities in any way and had always been very active in sports of all types. In 1950, he was examined in connection with playing football in school and was disqualified because he had a heart murmur. In March of 1952, he tried to enlist in the U. S. Navy, but was rejected because of the murmur. Football was his chief interest, and his ambition was to become a professional football player. The diagnosis of heart disease disturbed him greatly, and he was determined to have the trouble corrected so that he could remain active in sports. He gave no family history of heart disease. He had 4 brothers and 5 sisters living and well. His past history was that of measles, mumps, and chicken pox in early childhood. He had no history of rheumatic fever, but had several episodes of convulsions before he was 5 years of age.

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Examination.—The patient was a well-developed, well-nourished, young man about eighteen years old. His pulse was 72, respirations 20, blood pressure 118/76 mm. Hg, height 5 feet 8 inches, and weight 150 pounds. The general physical examination was all negative except for the examination of the chest which presented the following: There was definite cardiomegaly with point of maximum impulse 2 fingerbreadths to the left of the nipple line, in the sixth intercostal space.

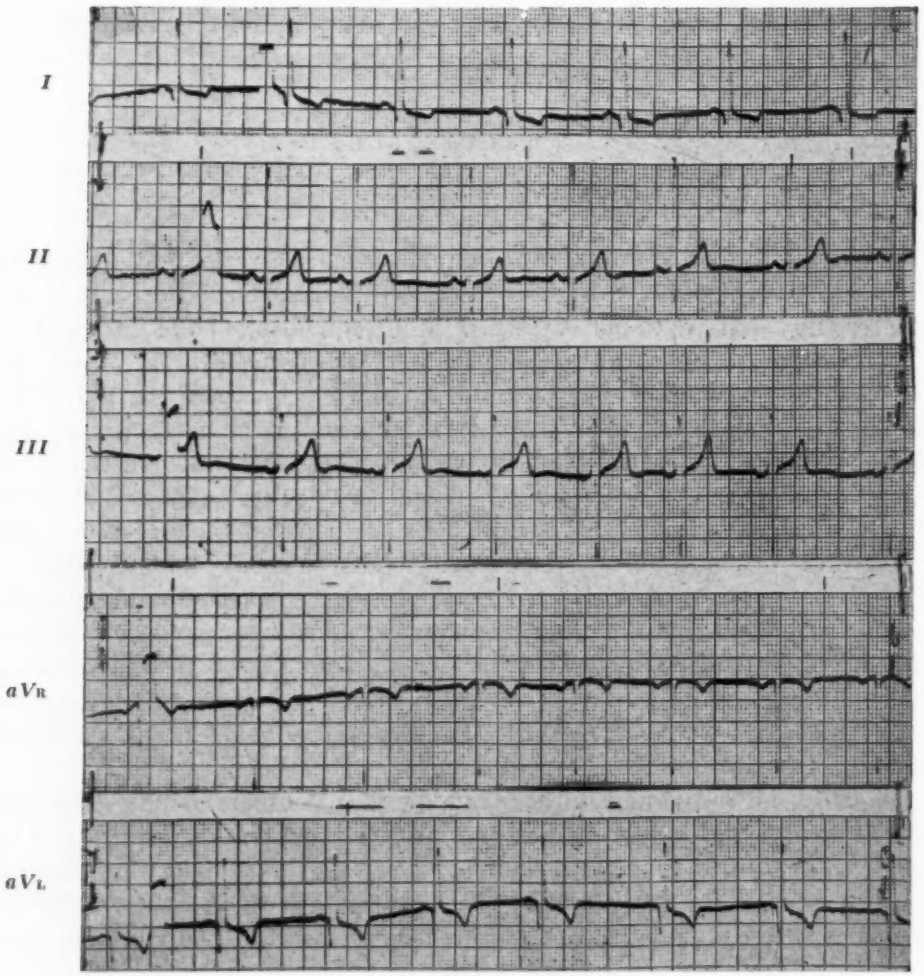

Fig. 1A.—ECG. Z.S.—Lead I: inverted T, prominent Q; Lead II: extrasystoles, prominent S; Lead III: increased amplitude, prominent S; aV_R: normal except increased amplitude; aV_L: inverted T and prominent Q.

There was a visual pulsation along the entire left of the sternum. There was a Grade 3 systolic murmur at the apex. At the pulmonic area, there was a Grade 3 systolic murmur with a reduplication of the second sound, and a Grade 4 diastolic blowing murmur. The murmurs gave the impression of a machinery-like murmur, and could be heard over the entire precordium with varying intensities. A fine thrill was palpable over the entire precordium to the left of the sternum. The electrocardiogram is shown in Fig. 1.

The patient was studied at a cardiac diagnostic center where various diagnostic procedures were carried out, including cardiac catheterization. The pertinent positive findings were summarized as follows: (1) left ventricular hypertrophy on electrocardiogram; (2) prominence of the outflow tract of right ventricle on fluoroscopic examination; (3) pulmonary hypertension, and right ventricular hypertension of moderate degree; (4) no evidence of an intracardiac shunt.

It was concluded that, while the catheterization data did not definitely indicate the presence of a patent ductus arteriosus, the auscultatory phenomena and associated clinical data indicated the presence of this congenital anomaly.

Treatment.—The patient was subjected to exploratory thoracotomy. At operation, the arch of the aorta was somewhat hypoplastic. The pulmonary artery was dilated. A systolic and diastolic thrill, which was much stronger during the systole, was palpable over the entire arch of the aorta and the pulmonary artery. It could be palpated into the root of the left lung and over the base of the heart. Patent ductus arteriosus, 7 mm. across, was found and was temporarily occluded. The heart action was observed. No ill effects were noticed. The ductus was then obliterated. Following the obliteration of the ductus arteriosus, the thrill was no longer palpable in the arch of the aorta, or in the pulmonary artery distal to the ductus. A very definite thrill was palpable, however, over the root of the pulmonary artery and the aorta, and over the base

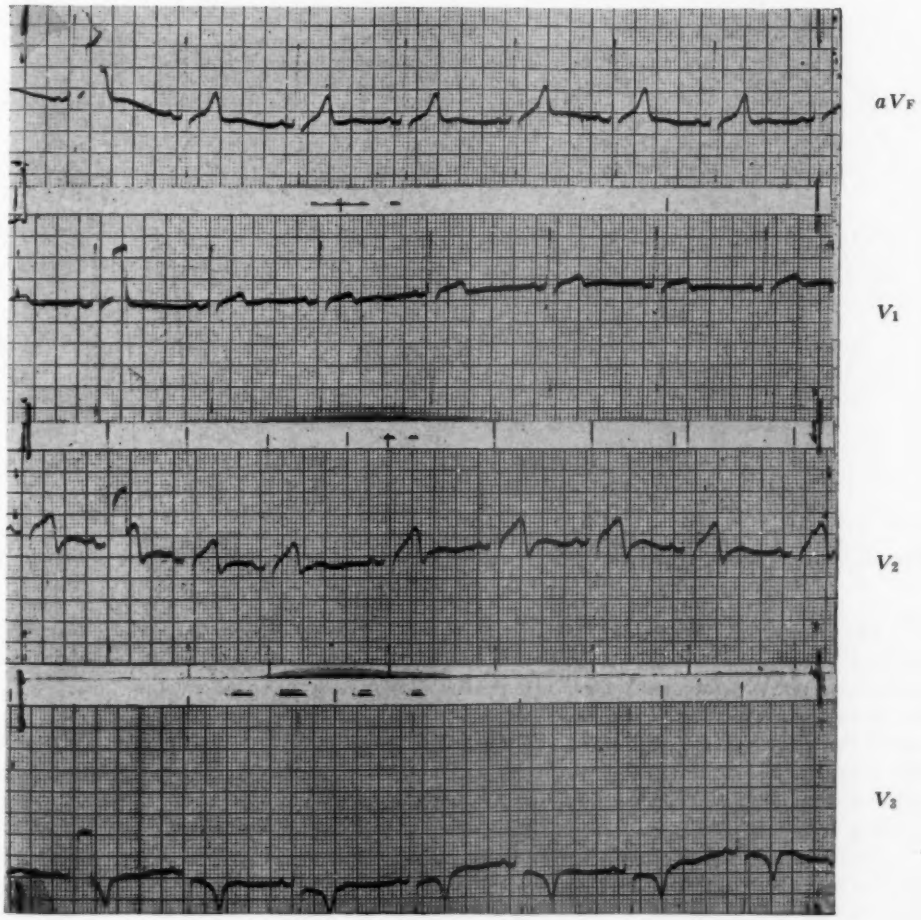

Fig. 1B.—ECG. Z.S.—aV_F,V_1 and V_2: increased amplitude; V_3: inverted T.

of the heart. It appeared to be strongest about an inch above the base of the heart, and was stronger in the pulmonary artery than in the aorta. With the pericardium open, the base of the heart, the root of the aorta, and the pulmonary artery were palpated and inspected. Epicardial fat appeared to be increased in amount. A continuous thrill, stronger during systole, was present throughout the cardiac cycle, and appeared to be strongest in the pulmonary artery, just above the base of the heart. The patient was thought to have an aorticopulmonary fistula. Limited

dissection between the aorta and the pulmonary artery was done, but thorough exploration of the area could not be carried out. The operation was discontinued, and the patient made an uneventful recovery.

Postoperatively, auscultation revealed a systolic and diastolic murmur, heard best next to the sternum in the left third intercostal space, but audible over the whole precordium. It was of decreased intensity when compared with the murmur the patient had before the operation. Similarly, a fine palpable thrill was still present over the precordium. The patient was symptom free, but again was barred from athletics, and was turned down in his new attempt to enlist in the U. S. Navy. Disappointed, he was very anxious that something more be done for him.

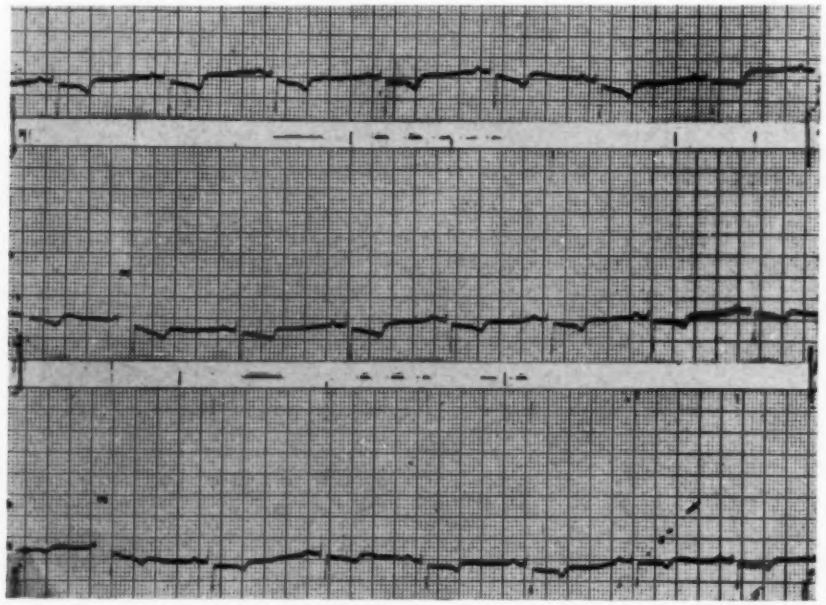

Fig. 1C.—ECG. Z.S.—V_4, V_5, and V_6: inverted T (heart strain; ventricular hypertrophy L > R)

The patient was reoperated upon 6 months after the ligation of the patent ductus. A thrill was again readily palpable over the root of the pulmonary artery, over the aorta, and over the base of the heart at the operation. The thrill was again stronger in the pulmonary artery, as it had been on previous exploration. Dissection was begun between the pulmonary artery and the root of the aorta. The previous operation made separation of anatomic structures very difficult. The aorta ballooned out and ruptured in a small area where its adventitia was inadvertently removed during the dissection between the root of the aorta and the pulmonary artery. The bleeding was controlled temporarily, but eventually it proved fatal to the patient.

Post-Mortem Examination.—The heart weighed 480 grams and measured 10 cm. from the base to the apex, and 10 cm. transversely at the base. The myocardium of the left ventricle measured 2 cm. in thickness. The myocardium of the right ventricle measured 9 mm. in thickness. The myocardium was reddish brown in color. All valve leaflets were thin, translucent, and freely movable. The aortic valve measured 5.7 cm., the mitral valve 8 cm., the tricuspid 11 cm., and the pulmonary valve 5.5 cm. in circumference at their attachment.

The right coronary artery originated in the aorta, in the right sinus of Valsalva, just above the attachment of the aortic valve leaflet, by an oval ostium 10 x 8 mm. About 1 cm. from the aorta this artery divided into circumflex and anterior descending branches (Fig. 2). The anterior descending branch, imbedded in epicardial fat, continued superiorly over the anterior border of the pulmonary artery forming a loop 34 mm. long. The artery was tortuous throughout, and on cut section it measured 5 mm. in diameter in the region of this loop. Its wall had the appearance

of a coronary artery in thickness and color. The descending branch of the right coronary artery continued in a corkscrewlike course downwards to within about an inch and a half of the apex where it made 2 branches which turned almost straight to the left. They each measured 1.5 mm. in the internal diameter, and again had the appearance of a normal coronary artery in thickness and color. They were each about 3 cm. in length, and fused to form 1 channel which anastomosed with the anterior descending branch of the left coronary artery. The right anterior descending coronary artery then continued over the apex where it broke up into numerous terminal branches. The circumflex branch of the right coronary artery was markedly dilated, measuring 10 mm. in the internal diameter. Its wall resembled an artery in thickness and color. It formed 3 loops between the base of the aorta and the right ventricle and right auricle, continuing thence in the auriculoventricular sulcus in a corkscrewlike, tortuous course towards the posterior interventricular septum.

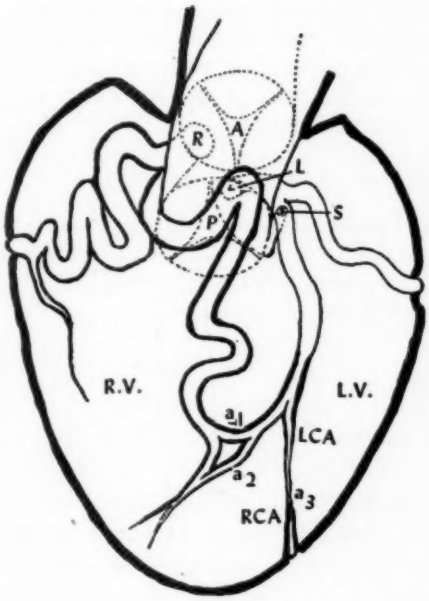

Fig. 2.

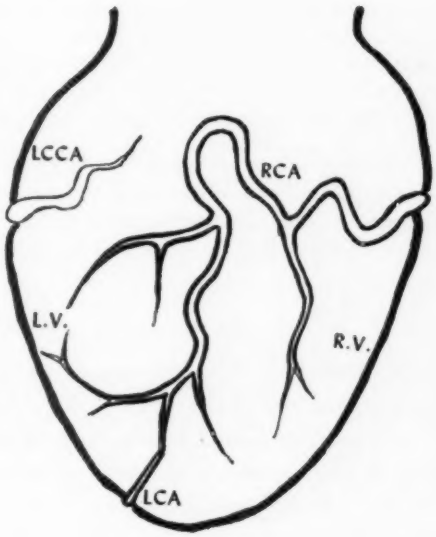

Fig. 3.

Fig. 2.—Z.S. Diagrammatic representation of coronary arteries, anterior view. *R.V.* = right ventricle; *L.V.* = left ventricle; *LCA* = left coronary artery; *RCA* = right coronary artery; a_1, a_2, a_3 = anastomosis between right and left coronary arteries; *S* = septal branch of left coronary artery; *A* = aorta; *P* = pulmonary artery; *R* = ostium of right coronary artery; *L* = ostium of left coronary artery. Right coronary artery wall resembles normal artery in thickness and color. Left coronary artery wall is veinlike except near point of anastomosis with the right coronary artery.

Fig. 3.—Z.S. Diagrammatic representation of coronary arteries, posterior view. *R.V.* = right ventricle; *L.V.* = left ventricle; *RCA* = right coronary artery; *LCA* = left coronary artery; *LCCA* = veinlike left circumflex coronary artery.

Its internal diameter became progressively smaller, and as it reached the level of the interventricular sulcus, on the posterior side of the heart, it still measured 7 mm. in its internal diameter. Just before it reached the interventricular sulcus, it gave a rather large branch, which then spread out and terminated in small branches over the posterior aspect of the right ventricle. The right circumflex coronary artery then formed a large loop at the level of the posterior interventricular septum where it divided into 2 branches, each measuring 4 mm. in their internal diameter. One continued in a corkscrew manner over the posterior interventricular septum towards the apex. There it terminated in numerous branches spread out over the right and the left ventricles. One of these branches anastomosed with a terminal branch of the left anterior descending coronary artery. The other terminal branch of the right circumflex coronary artery spread out into several terminal branches over the posterior wall of the left ventricle (Fig. 3).

The left coronary artery originated from the pulmonary artery, the left posterior side, by an ostium 7 x 5 mm., located 15 mm. above the point of attachment of the valve leaflets. It continued to the left, behind the pulmonary artery and emerged anteriorly, between the left auricle and the root of the pulmonary artery. It measured 22 mm. in length and 10 mm. in its internal diameter. Its wall was thin, veinlike in appearance. It divided into the anterior descending and the circumflex coronary arteries, each being of about equal size, each veinlike paper-thin in appearance, and each measuring 5 mm. on the internal diameter at the point of origin. The anterior descending branch was saccular and tortuous. It continued in a downward course, towards the apex, forming several minor loops. At the point of origin from the left coronary artery, it divided into 2 branches, each measuring 4 mm. in diameter. One branch dipped immediately, deep into the interventricular septum where it broke up into many zigzagged channels, varying in size from 3 to 5 mm. in diameter. These honeycombed the entire anterior half of the interventricular septum. Several of them were found to communicate with the left intraventricular cavity by openings varying from 1 to 2 mm. in diameter. The left anterior descending coronary artery became thick walled about half way between the apex and the base of the heart, and took on the appearance of an artery (Fig. 2). Soon it divided into 2 branches, each 3 mm. in the internal diameter. One of these anastomosed with a similar branch from the right anterior descending coronary artery. The other continued over the apex where it anastomosed with a branch of the right circumflex coronary artery. The left circumflex coronary artery was short and veinlike throughout.

Microscopic Examination.—The myocardial fibers appeared markedly hypertrophic. There was moderate hydropic degeneration of the myocardial fibers. Marked interstitial fibrosis, with large areas of dense scarring, was also seen. The coronary vessels were moderately sclerotic, and small accumulations of mucin were observed in the media and the subintima.

DISCUSSION

Embryologically, the coronary arteries appear in the 12 mm. embryo as 2 minute openings in the wall of the truncus arteriosus. In an embryo of this size, the truncus arteriosus is an elongated tube between the level of the sixth aortic arch and the coronary sulcus. A spiral ridge of endothelium develops inside the truncus arteriosus and divides it into 2 channels, the aorta and the pulmonary artery. Normally, this division takes place in such a manner that both of the minute coronary ostia are located in the aorta. An error in the development of the spiral septum in the truncus arteriosus can result in one or both of the ostia of the coronary arteries being located in the pulmonary artery.[7]

Review of the reports of the adult type of anomalous left coronary artery originating in the pulmonary artery indicates that this anomaly leads to hypertrophy of the heart, primarily the left ventricle.

Electrocardiogram was reported in only 1 of the adult cases with anomalous left coronary artery recorded in the medical literature.[6] It showed normal sinus rhythm, rate 72 per minute, and left axis deviation with bundle branch conduction defect. S-T_1 was depressed. There was deep S_2 and biphasic T_4. It did not present the inverted T waves seen in the infant cases. Clinical symptoms of heart disease were present in only 18 per cent of the reported cases. Yet, the average age of these patients at the time of death was only 35 years. Forty-five per cent of these patients never reached the age of 30 years. Only 27 per cent lived past 50 years of age. Death was sudden and unexpected in 82 per cent of these patients. Death came when these people were thought to be in good health (Table I).

TABLE I. LEFT ANOMALOUS CORONARY ARTERY—ADULT TYPE

AGE*	AUTHOR	MYOCARDIAL HYPERTROPHY	FIBROSIS OF MYOCARDIUM	MYOCARDIAL SCARS—OLD INFARCTS	ANEURYSMAL DILATATION OF VENTRICLE	CALCIFICATION IN MYOCARDIUM	DILATATION OF CORONARY ARTERY	ARTERIOSCLEROSIS IN CORONARY ARTERY	THIN, VEINLIKE LEFT CORONARY ARTERY	TORTUOUS CORONARY ARTERIES	ANASTOMOSIS BETWEEN RIGHT AND LEFT CORONARY ARTERY	SINUSOIDS	ACCESSORY CORONARY ARTERY	PREVIOUS HEART DISEASE	SUDDEN DEATH
60	Abbott	+	+				+		+	+			+		
38	Kockel	+					+			+				+	+
27	Rubbert	+					+		+	+					+
57	Dietrich	+						+			+			+	
17	Orsos	+	+	+			+								+
30	Ruddock		+			+	+				+	+			+
32	Helpern	+	+	+			+			+		+			+
27	Gouley		+			+	+		+	+		+			+
27	Wuethrich	+	+	+	+	+	+	+		+	+	+	+		+
16	Rotter	+	+	+			+	+	+						+
58	Rotter	+	+	+			+	+	+						+
Per Cent		82	73	45	9	27	91	36	45	55	27	36	18	18	82

*Average age 35 years.

Post-mortem examination of these hearts revealed left ventricular hypertrophy, right coronary preponderance, and dilatation and tortuosity of the coronary blood vessels described as simulating cirsoid aneurysms in most of these patients. Grossly visible anastomosis between the right and left coronary arteries were seen in 27 per cent of these hearts; and in 36 per cent, dilated sinusoidal channels were seen in the interventricular septum, as well as direct communication between the intraventricular cavity and the left coronary artery. Blood flow, at least in part of the left coronary artery in these patients, appears to have been from the myocardium into the pulmonary artery. This left the supply of the myocardium with oxygenated blood to the right coronary artery and the communicating channels carrying blood directly from the cavity of the left ventricle into the myocardial sinusoids and the connecting branches of the coronary arteries. The right coronary artery was enlarged in these hearts, carrying increased amounts of blood to the myocardium. The left coronary artery was veinlike, at least in part, and undoubtedly acted in part as a vein carrying blood from the myocardium into the pulmonary artery.

Our patient presented the markedly enlarged, tortuous right coronary artery commonly seen in these hearts, and, as well, the definite and prominent anasto-

motic communications between the right and left coronary artery. He also had intricate networks of endothelial sinusoids in the anterior half of the interventricular septum, which appeared to be a direct continuation of the septal branch of the left coronary artery, and which communicated with the left ventricular chamber by numerous openings. In addition, a small patent ductus arteriosus was present. This was not described in any of the reported cases of adult patients with anomalous left coronary artery. Ligation of this ductus produced no clinically discernible ill effects. Actually, this patient had 2 arteriovenous communications, namely, the patent ductus and the left coronary artery.

In the adult patients with anomalous left coronary artery, the only clinical findings may be: (1) myocardial hypertrophy, and (2) abnormal electrocardiographic findings. Symptoms of heart disease generally have been absent in the reported cases. Because these patients are usually asymptomatic, the cardiomegaly may be found only on some routine physical examination or on a mass survey by x-ray. Cardiac enlargement and electrocardiographic evidence of myocardial hypertrophy and coronary insufficiency in a young adult with no cardiac symptoms should make us suspect the presence of this congenital anomaly.

SUMMARY

A case of anomalous left coronary artery, adult type, with patent ductus arteriosus was reported.

Obliteration of the patent ductus resulted in no clinically demonstrable ill effects in this patient.

Patients with anomalous left coronary artery reaching adult life are usually symptom free, but their average life span is only 35 years.

Myocardial hypertrophy and abnormal electrocardiograms are usually the only clinically demonstrable evidence of heart disease in these patients.

The cardiac findings in 11 reported cases of the adult type of anomalous left coronary artery were summarized.

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CARDIAC INJURY PRESUMABLY DUE TO USE OF THE EXTERNAL ELECTRIC CARDIAC PACEMAKER IN STOKES-ADAMS DISEASE

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The purpose of this report is to draw attention to the occurrence of possible injury to the heart with the use of the external electric cardiac pacemaker.

CASE REPORT

L. L. (M. H. 77328), a 75-year-old white male was admitted to Montefiore Hospital on Dec. 8, 1955, because of recurrent seizures of 48 hours' duration. Six months prior to admission, an episode of brief and unexplained unconsciousness with convulsions had occurred. He was well in the interim. At the time of admission, seizures were occurring every 5 to 15 minutes.

Past medical history included a left nephrectomy and ureterectomy for malignant ureteral papilloma 13 years ago. He had been given postoperative irradiation with apparent cure. He had known diabetes mellitus, controlled by diet alone, for 8 years. There had been no prior history or symptoms of cardiac disease.

Physical examination on admission revealed an acutely ill, well-developed and well-nourished elderly white man. Blood pressure was 170/30 mm. Hg, pulse was regular at 28 beats per minute. Respiratory rate was 20 per minute, and rectal temperature was 100° F. No significant abnormalities of the head and neck were present. The anteroposterior diameter of the chest was increased, and diffuse rhonchi were noted in both lung fields. The heart size was indeterminate and the heart sounds could not be heard. The liver edge was palpable 1 cm. below the right costal margin. The extremities were normal without edema. The neurologic examination was normal except for transient slight droop of the right angle of the mouth subsequent to seizures.

Laboratory Data.—The hematocrit was 50 per cent, and the white blood count 16,000, with 84 per cent polys. Urinalysis was normal except for 3+ glycosuria. The serologic test for syphilis was negative. Blood urea nitrogen was 48.4 mg. per cent on admission and rose to 70 mg. per cent 48 hours later. Fasting blood sugar was 447 mg. per cent, and serum acetone was negative. Serum electrolytes were normal except for an initial CO_2 content of 17.3 meq. per liter, which rose to 27 meq. per liter 48 hours later. Serum calcium was 9.8 mg. per cent; phosphorus 4.0 mg. per cent; alkaline phosphatase 2.7 Bodansky units; acid phosphatase 0.1 Bodansky units; cholesterol/esters 236 mg. per cent/177 mg. per cent. A portable roentgenologic examination of the chest showed a slight degree of central and peripheral pulmonary congestion, left ventricular enlargement, and tortuosity of the aorta. The initial electrocardiogram revealed complete heart block with an auricular rate of 116 and a ventricular rate of 24 beats per minute.

Hospital Course.—Continuous electrocardiographic observations were made. The mechanism of the development of the Stokes-Adams seizures was documented repeatedly as ventricular stand-

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still in the course of complete atrioventricular dissociation. Initial treatment with sublingual Isuprel, atropine, sedation, hydration, and O_2 inhalation was followed by improvement, with a decrease in frequency of ventricular standstill and seizures. During the episodes of ventricular standstill, chest pounding frequently brought about instantaneous return of ventricular contraction. Following 24 hours of initial improvement, seizures returned with increasing frequency and more prolonged duration. Asystole occurred about every 2 minutes and lasted as long as 47 seconds. The asytole was now refractory to epinephrine and its analogues. The patient became semicomatose, cyanotic, and manifested Cheyne-Stokes respiration. No blood pressure was obtainable. At this point the external electric cardiac pacemaker was applied.* The electrodes were placed at the fourth intercostal space to the left of the sternum and in the fifth intercostal space at the left anterior axillary line. Almost immediately following the use of the pacemaker, the patient was dramatically revived. After initial stimulation at 100 volts and at a rate of 60 impulses per minute, a gradual reduction in magnitude to 50 volts was accomplished. This was found to be an effective voltage and rate to maintain the blood pressure at 120/60 mm. Hg. After the patient had been on the pacemaker for several hours at the above voltage and rate, it was noted that the pulse pressure widened, the blood pressure going from 120/60 to 140/40 mm. Hg. By increasing the rate of the pacemaker to 75 impulses per minute and keeping the voltage constant at 50 volts, it was possible to bring the blood pressure back to 120/60 mm. Hg.

It was observed that each stimulus of the pacemaker discharged the respiratory musculature of the left hemithorax. This had the effect of interfering with the patient's own respiratory efforts and necessitated frequent tracheal suction. During the remaining 40 hours of life, the patient's heart produced only sporadic, ineffectual contractions when given a trial off the pacemaker.

Twenty-four hours after the application of the pacemaker, a loud apical pericardial friction rub was heard for the first time. From then on, the patient's condition deteriorated with the onset of deepening coma, even though the blood pressure remained stable until the end. Death occurred 16 hours after the friction rub was noted.

Post-Mortem Examination.—On gross examination, two superficial fresh burns of the skin of the precordium, 2 cm. in diameter, were seen; one at the fourth intercostal space just to the left of the sternum, the other at the fifth intercostal space in the anterior axillary line. The pericardial sac interiorly and exteriorly showed some areas of hemorrhage, predominantly on the left side, corresponding to the location of the burns on the chest wall. There was no evidence of pericarditis.

The heart weighed 525 grams. It was moderately enlarged due to hypertrophy and dilatation, chiefly of the left ventricle. Areas of congestion and hemorrhage were present in the epicardium and subepicardial fat, mainly on the anterior aspect and external border of the left ventricle, corresponding to the described pericardial lesions. Some areas of endocardial thickening were seen over the interventricular septum and left ventricular endocardium. There were small atheromatous deposits in the aortic and mitral valves. A minimal degree of interstitial scarring was seen on section of the interventricular septum. A moderate degree of coronary arteriosclerosis without obstruction was seen.

Moderate to marked visceral congestion was found in the lungs, spleen, liver, and kidney.

The microscopic examination of the heart revealed fibrosis of the bundle of His, areas of hemorrhage, and swelling of some of the elastic fibers of the pericardium. Microscopic examination of the diaphragm showed small areas of hemorrhage in its pleural surfaces.

Sections taken from the precordial skin and musculature in the sites of application of the electrodes showed some areas of erosion of the epidermis, round cell infiltrates, and vascular congestion. The dermal collagen was slightly swollen and acidophilic, with occassional bluish areas.

Examination of the central nervous system showed minimal anoxic ganglion cell loss in Ammon's horn.

An incidental finding was a circumscribed 5 cm. hypernephroma of the remaining right kidney, without evidence of metastases.

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*Manufactured by Electrodyne Co., Inc., Norwood, Mass.

COMMENT

This patient with Stokes-Adams disease was refractory to the usual pharmacologic management, and in extremis when revived by the external electric cardiac pacemaker developed by Paul Zoll.[1,2]

Complications arising from use of the pacemaker have been noted to include pain produced by electrical stimulation, local skin burns at the area of electrode application, and interference with respiration due to discharge of respiratory musculature.

Rose and Wartonick[3] described a patient with Stokes-Adams disease who was treated intermittently for 46 days with the pacemaker, and in whom evidence of mild pericarditis was found at autopsy. These authors felt that the pericardial changes might have been due to repeated and prolonged stimulation by the pacemaker. However, Zoll did not find pericardial damage even with voltages up to 125 volts, as recorded on the pacemaker.[4]

The development of a pericardial friction rub and the autopsy findings of pericardial and epicardial injury in our patient may represent electrical injury caused by the pacemaker. This is further substantiated by the position of the injuries in relation to the external placement of the electrodes. More remote explanations of the cardiac damage might include anoxia occurring during the course of ventricular standstill or the pounding of the chest wall.

SUMMARY

1. A case of Stokes-Adams disease has been reported in which the external electric cardiac pacemaker was used with temporary resuscitation.

2. Pericardial damage from use of the pacemaker was suspected during life, and pericardial and epicardial damage was found at autopsy.

3. This cardiac injury may have resulted from electrical effects of the artificial pacemaker.

We are indebted to Dr. Dennison Young and Dr. John B. Schwedel for their aid in the management of this case. We wish to thank Dr. Louis Leiter, Chief of the Division of Medicine, and Dr. H. M. Zimmerman, Chief of the Division of Laboratories, Montefiore Hospital, for reviewing this paper.

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ALTERNATING BIDIRECTIONAL TACHYCARDIA

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BIDIRECTIONAL tachycardia can still be considered an uncommon arrhythmia. Since the excellent review of 32 patients by Zimdahl and Kramer[1] in 1947, only 3 additional cases have appeared in the medical literature.[2,3,4] The mechanism of the production of this arrhythmia remains controversial. However, the poor prognosis associated with the presence of bidirectional tachycardia is uniformly recognized.

The purpose of this report is to show the response of bidirectional tachycardia to the Valsalva maneuver and oral potassium chloride.

CASE REPORT

W. R., a 45-year-old, unemployed Negro man was admitted to the medical service of the District of Columbia General Hospital on Mar. 16, 1956, with the chief complaint of severe shortness of breath of 2 days' duration.

In 1952, he had been treated at another hospital for a period of 2 months for an acute myocardial infarction. Chronic congestive heart failure, manifested by exertional dyspnea and persistent lower extremity edema, had required the daily administration of 0.1 Gm. of digitalis leaf and the periodic administration of diuretics since 1952. There was no past history of hypertension.

On admission the physical signs were: Temperature: 37°C., orally; Pulse: 130/min.; Respirations: 40/min.; Blood pressure: 120/80 mm. Hg. He appeared acutely ill and severely dyspneic. Examination of the ocular fundi revealed moderate narrowing and increased tortuosity of the arterioles. Cervical venous distention was marked. Marked cardiomegaly to the left was evident. The second pulmonic sound was increased in intensity. A Grade 2 blowing apical systolic murmur was present. Fine and medium inspiratory râles were noted bilaterally. The lower right lung field was dull to percussion and breath sounds were diminished in this area. The liver edge was 12 cm. below the right costal margin in the mid-clavicular line. Moderate ascites and marked pitting edema of the lower extremities were observed.

Laboratory data included the following: hematocrit: 39; hemoglobin: 13 Gm.: white blood count: 8,850, with a differential count of 65 neutrophils and 35 lymphocytes; blood urea nitrogen: 32 mg. per cent; total serum protein: 7.0 Gm. with albumin of 4.0 Gm. and globulin of 3.0 Gm.; fasting blood sugar: 105 mg. per cent. Chest x-ray demonstrated cardiomegaly with left ventricular preponderance, pulmonary congestion, and a right hydrothorax.

On admission, the electrocardiogram revealed atrial fibrillation with a rapid ventricular response and an initial 0.04 second deformity of the QRS complex, suggesting the presence of an old diaphragmatic myocardial infarction (Fig. 1).

Hospital Course.—On the day of admission, 0.6 mg. of lanatoside C given intravenously slowed the ventricular response to 106 per minute. He was then given 0.25 mg. of digoxin orally

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twice daily. Forty-eight hours after admission, and after receiving a total of 1.0 mg. of digoxin by mouth, a repeat electrocardiogram revealed alternating bidirectional tachycardia (Fig. 2). Carotid sinus pressure did not alter the arrhythmia. However, the Valsalva maneuver produced the effect illustrated in Fig. 2. Digitalis was discontinued. Oral potassium chloride in a single dose of 5.0 Gm. abolished the arrhythmia 25 minutes later. Potassium chloride in the amount of 2 Gm. every 3 hours successfully controlled the arrhythmia for at least 6 hours. The patient was found dead 15 hours after the start of potassium chloride therapy. Autopsy was not granted.

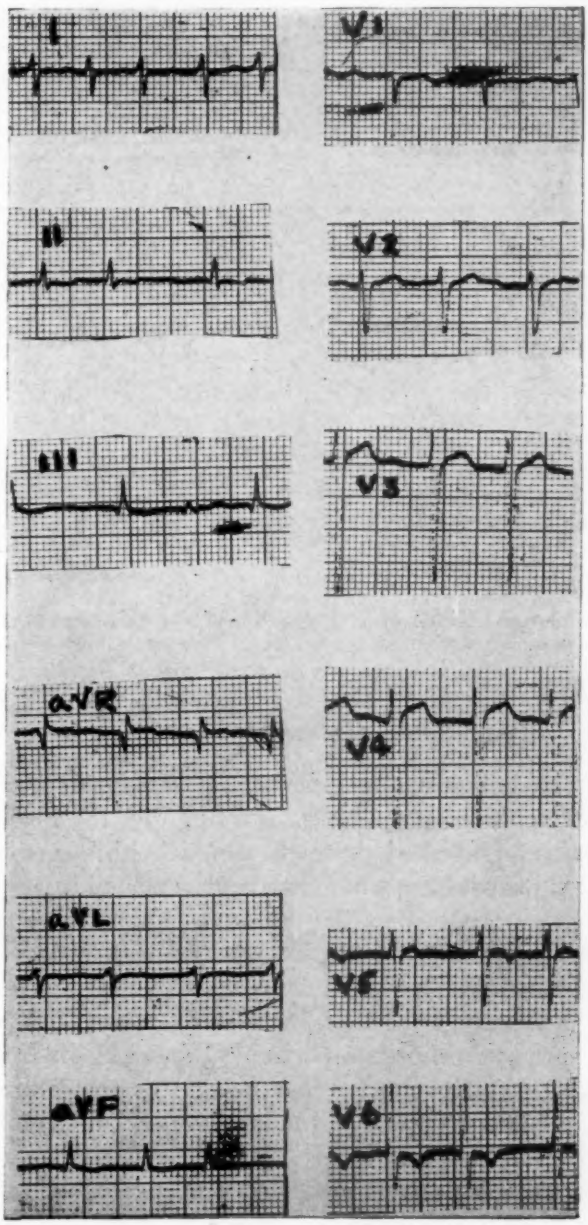

Fig. 1.—Electrocardiogram taken Mar. 16, 1956. (See text.)

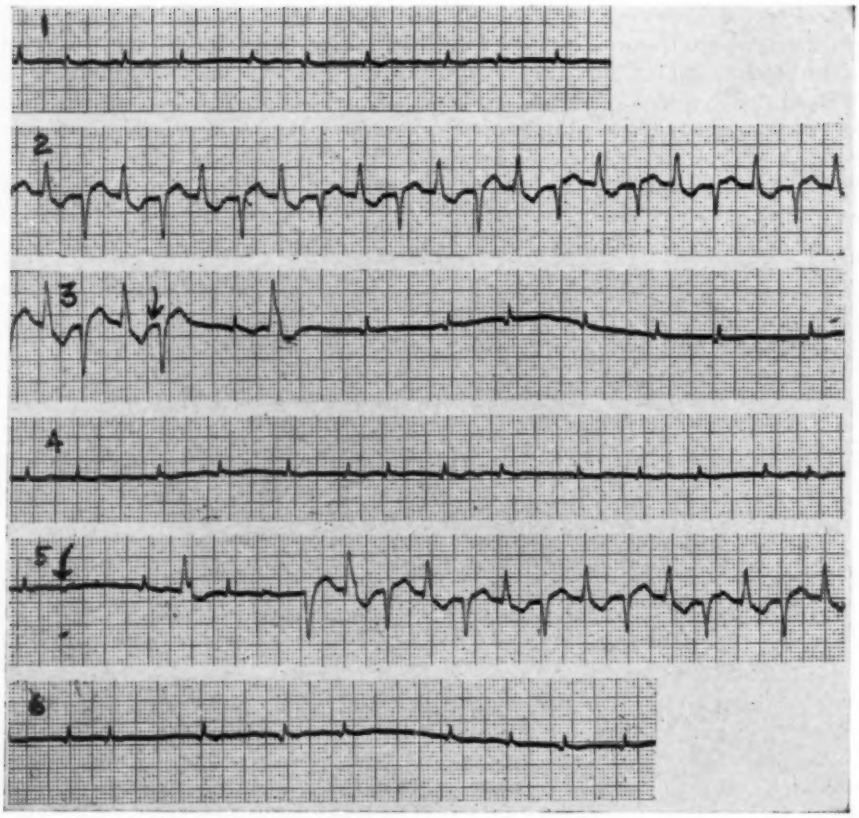

Fig. 2.—Strips 1 through 5 are continuous records of Lead III. The arrow in strip 3 denotes the onset of the Valsalva maneuver, and the arrow in strip 5 indicates the release of the Valsalva. Strip 6 is again Lead III, 25 minutes after the first dose of KCl. (See text.)

DISCUSSION

The effect of the Valsalva maneuver upon alternating bidirectional tachycardia has not been reported previously. Presumably the mechanism by which the Valsalva maneuver abolished the arrhythmia in this case is similar to that induced by carotid sinus pressure which has been reported by several authors.[3,4,10]

It is interesting to note that neither left or right carotid sinus massage altered the arrhythmia in this case. Perhaps the lack of effect of carotid sinus massage was related to the unusually short and thick neck of the patient.

The effect of potassium chloride in abolishing the arrhythmia at least temporarily has been noted in previous reports.[2,3] Likewise, the frequent occurrence of digitalis intoxication in the reported instance of this arrhythmia has been noted previously.[3,4] The salutary effect of potassium upon arrhythmias induced by digitalis is now well established.

In our patient, the Valsalva maneuver simultaneously abolished both the upwardly and downwardly directed complexes by reverting the rhythm to the pre-existing atrial fibrillation. This would suggest that the focus of impulse information responsible for the alternating bidirectional tachycardia was sus-

ceptible to the influence of reflex activity, and, therefore, located supraventricularly. The normal time required for depolarization (0.08 to 0.09 second) for both the upward and downward complexes suggests that impulse formation arose above the level of the bifurcation of the bundle of His.

The R-R interval of the upwardly directed complexes was equal to that of the downwardly directed complexes (0.72 second). The interval between the upwardly directed complex and the succeeding downwardly directed complex was precisely 0.36 second, indicating an equal length of ventricular diastole for both the upward and downward complexes. The concept of a single focus responsible for both the downward and upward complexes is favored by the finding of identical ventricular rates and identical periods of ventricular diastole.

These observations suggest that the mechanism of the arrhythmia in this case may be due to alternate conduction down the left and right branches of the bundle of His of an impulse which arises from a single focus above the level of the bifurcation of the bundle.

Since the points cited above in support of the postulated mechanism in this case are not all present in the previously reported cases, it seems reasonable to assume that more than one mechanism may operate to produce an arrhythmia with alternating upward and downward complexes. The use of the designation of "alternating bidirectional tachycardia" is suggested to exclude those cases of ventricular tachycardia with runs from multiple intraventricular foci and to avoid qualifying terms which imply a single mechanism of production.

SUMMARY

A case is reported of alternating bidirectional tachycardia in which the beneficial effect of the Valsalva maneuver and oral potassium chloride was demonstrated.

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PAROXYSMAL TACHYCARDIA WITH 2:1 EXIT BLOCK

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EXIT block has long been known to occur in slow parasystolic rhythms.[1] Nevertheless, there are few reported clinical cases in which an automatic center, firing at rapid rates, can develop a systematic 2:1 exit bolck.[2,3] Two of such cases were observed recently in our department. In one, the paroxysm arose in the ventricles, and in the other it was produced in the atria.

1. *Paroxysmal Ventricular Tachycardia With 2:1 Exit Block.*—The upper record of Fig. 1 shows the control tracing (Lead II) of a 60-year-old patient with coronary sclerosis. Sinus rate is 75 per minute and the P-R interval is 0.14 second.

In the lower tracing, an automatic ventricular rhythm appears, with a rate ranging from 75 to 78 per minute, which is approximately the same as the sinus rate. As the paroxysm originates in the ventricles, fusion beats are seen at its beginning and at its end (second and eighth ventricular complexes). In Fig. 2, both records are continuous tracings of the same patient as in Fig. 1. At the beginning of the lower strip, a sinus beat is interpolated between two ventricular complexes, without disturbance of the ectopic rhythm. The R-R interval is approximately 0.78 second, corresponding to a rate of 77. The P-R interval of the sinus beats is lengthened to 0.24 second, as compared with its usual duration of 0.14 second. This lengthening is a common finding after interpolated ventricular premature systoles. Posteriorly to the fifth normal ventricular complex, the automatic rhythm suddenly doubles its rate until the end of the tracing. This can best be explained by considering the previous existence of a 2:1 exit block, which permitted, alternatively, only every second impulse to emerge. The resultant picture is that of a ventricular tachycardia with an independent sinus rhythm.

2. *Paroxysmal Atrial Tachycardia With 2:1 Exit Block.*—The upper tracings in Fig. 3 (Leads II and VI) were obtained from a 45-year-old Negro with coronary sclerosis and congestive heart failure. Lower tracings correspond to the same patient after he had received 1.4 Gm. of powdered digitalis leaf in two doses, 6 hours apart. An atrial tachycardia has appeared with a rate of 150 per minute. The P-R interval is 0.18 second. Note that the morphology of the P waves is different from that observed during sinus rhythm.

At the beginning of Fig. 4, four atrial beats of the paroxysm can be seen, at its usual rate. After them, the next P wave fails to appear at the expected time (P-P interval of 0.40 second), but does so at an interval which is exactly twice (0.80 second) the normal distance. This phenomenon persists until the end of the record and is due to the presence of a 2:1 exit block which creates an impedance to the appearance, alternatively, of every second atrial stimulus. The fourth, sixth, eigth, tenth, and eleventh ventricular complexes are not conducted from the atria. They are present only after the appearance of the exit block, and are explained in the following way: 0.52 second after the last supraventricular inpulse transverses the A-V junction, the A-V node discharges automatically, its retrograde conduction to the atria being blocked as seen in the diagram.

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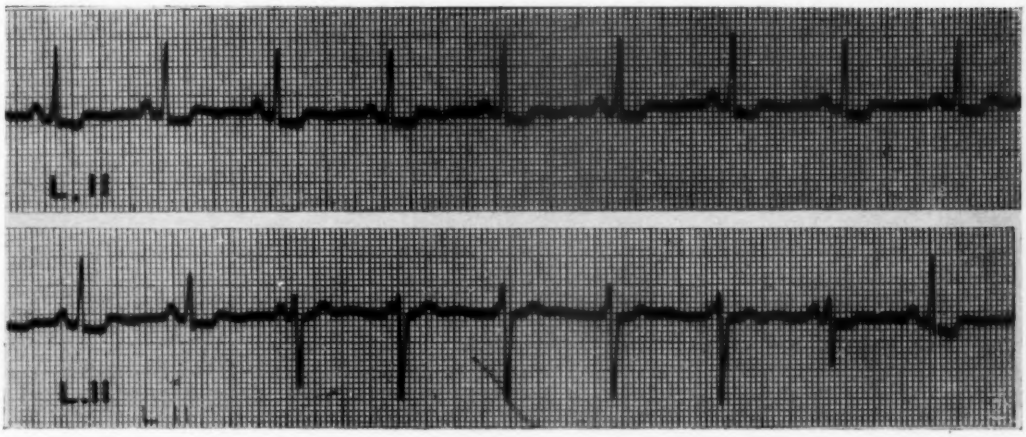

Fig. 1.—Case 1. Upper tracing: Normal sinus rhythm. Lower tracing: Appearance of an automatic ventricular rhythm.

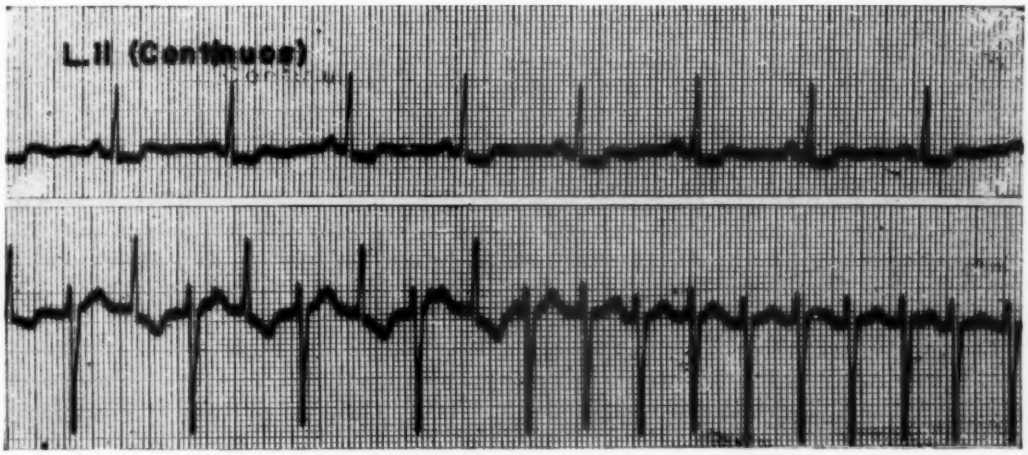

Fig. 2.—The automatic rhythm doubles its rate. This is due to the disappearance of a previous 2:1 exit block; every impulse now emerging.

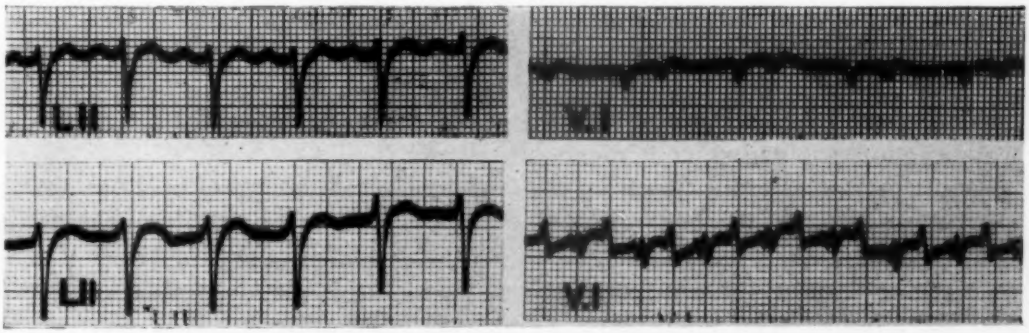

Fig. 3.—Case 2. Upper records: Control tracing. Lower records: Paroxysmal atrial tachycardia due to digitalis poisoning.

Consequently, the following P wave is transmitted with a longer P-R interval (0.32 second) than usual (0.18 second) and with greater degree of aberration, due to incomplete recovery of the right branch, for the R-P interval shortened to 0.08 second. At close inspection, the nodal beats are seen to have the same morphology as those of the supraventricular ones before the establishment of the exit block (fifth and last ventricular complexes), and only when the P waves merge in the QRS complexes do they change their form. Therefore, the deformity is not produced by aberrant ventricular conduction.

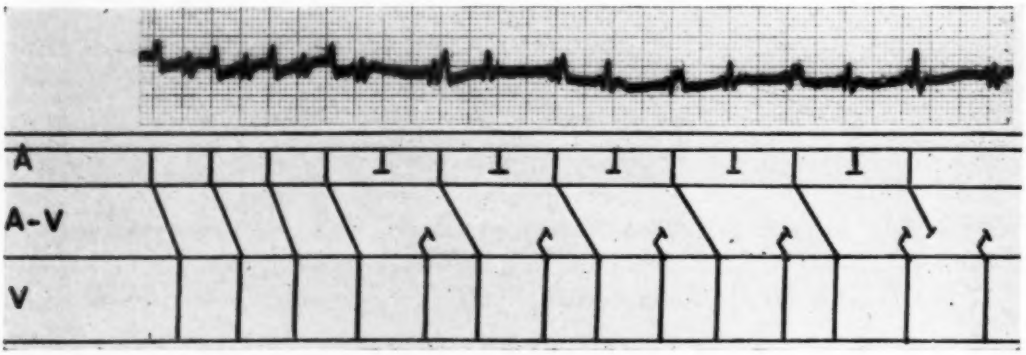

Fig. 4.—Lead V_1: Dissociation with interference in the presence of paroxysmal atrial tachycardia with 2:1 exit block, and concealed A-V conduction.

At the extreme right, the rate of discharge of the A-V nodal pacemaker can be measured, as the last P wave is located in such a portion of the cardiac cycle (as determined by the R-P interval of 0.02 second) that it cannot transverse the A-V junction completely. Nevertheless, it penetrates enough distance so as to reach the pacemaker, depressing it slightly. In fact, the last nodal complex appears 0.56 second from the preceding, instead of the 0.52 second usually seen throughout the tracing. This is due to the incomplete penetration of the P wave, that is, the effect of a blocked impulse on the formation of a subsequent impulse. This phenomenon has been named concealed conduction by Langendorf.[4] Thus, in this record there are two active pacemakers in operation, one in the atria (rate: 150 per minute), and one in the A-V node (rate: 108 to 115 per minute). As a whole, it can be considered an instance of A-V dissociation with interference in the presence of paroxysmal atrial tachycardia with 2:1 exit block, and concealed A-V conduction.

COMMENT

In clinical cases, 2:1 exit block during atrial tachycardia was observed by Camp and Scherf.[2] Also, Katz[5] reported the existence of atrial parasystole with exit block, before a paroxysm of atrial flutter; the atrial rate was identical on both occasions. These authors attributed the ectopic rhythms to focal impulse formation, for exit block is a property of automatic centers,[1,10] Circuitous movement or re-entry could not be responsible for the tachycardia, for a circulating wave cannot stop and start again spontaneously.

In a previous publication from our department[6] the effects of procaine amide on paroxysmal atrial tachycardia with second degree A-V block due to digitalis poisoning were analyzed. Noted were, first, the establishment of 1:1 A-V conduction; and, second, a gradual slowing of the atrial rate (to values as low as 130 per minute) with progressive paradoxical shortening of the P-R interval, until sinus rhythm was produced. Because of this behavior, its similarity with experimental ectopic atrial rhythms produced by electrical stimulation was

stressed. We concluded that digitalis tachycardia was due to automatic impulse formation, and the findings in Case 2 of this report tend to confirm our impression.

It is to be understood that it is not claimed that all atrial ectopic rapid rhythms have the same genesis, for, experimentally, other mechanisms have been postulated.[7-9] Although produced by various agents in the experimental animal,[3,12] proved cases of ventricular tachycardia with exit block are rare in the human being. Katz and Pick list 3 in a recent publication (Reference 9, Figs. 194, 196, and 214). Nevertheless, their cases show intermittent exit block, and were so diagnosed, because in all of them sinus beats appeared between the paroxysms, and, most important, because the pause between those paroxysms were exact multiples of the short intervals which separated the ectopic beats.

One case of ventricular tachycardia with varying exit block was reported by Scherf (Reference 3, Figure 108). It is interesting to note that his tracings also presented evidence of disturbances of conduction of the ectopic impulse, which are observed occasionally in experimental[10] as well as in clinical[11,13] parasystole. However, none of the above-mentioned electrocardiograms had a fixed 2:1 exit block, such as shown in Figs. 1 to 4.

SUMMARY

The presence of 2:1 exit block was definitely established in 2 patients, one with an atrial, and the other with a ventricular tachycardia. Since this phenomenon is a property of automatic rhythms, both paroxysms were ascribed to focal impulse formation. Nevertheless, this mechanism is not to be attributed to all ectopic rhythms.

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REPEATED CARDIAC ARRHYTHMIA DURING ETHER ANESTHESIA

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VARIOUS cardiac arrhythmias during ether anesthesia have been reported over the last 30 years. In laboratory investigations both rats[1] and dogs[2] have exhibited ventricular tachycardia and ventricular fibrillation. The abnormal rhythms in man have consisted of sinus arrhythmia, extrasystole, atrioventricular nodal rhythm, intraventricular block, and displacement of pacemaker.[3-6] In addition, "sensitivity" or "allergy" to ether has been noted in patients who developed general circulatory collapse and swelling about the ears and face when anesthetized with ether.[7,8]

Although attention has been called to irregular cardiac activity in children during congenital heart surgery, the incidence of arrhythmias during other procedures has been low. Stephen[9] notes the occurrence of brief episodes of cardiac irregularity due to endotracheal intubation and similar stimulation.

The present report concerns a recently encountered case which seems of significance due to its striking and recurrent nature, and to the fact that it was not associated with any of the usual precipitating causes.

CASE REPORT

A 6-year-old girl was admitted to the Children's Medical Center on Nov. 12, 1955, with a diagnosis of pseudarthrosis of the left tibia and fibula. Eighteen months prior to this admission an osteotomy and bone-grafting operation had been performed under open drop ether without complications. Nine months prior to admission tonsillectomy was performed with Vinethene induction followed by ether insufflation. Again there were no known cardiac complications. Five months previously a second bone-grafting procedure was attempted. Preoperative sedation consisted of Nembutal 100 mg. by rectum, and atropine 0.4 mg. and morphine 4.0 mg. subcutaneously. Anesthesia was induced with Vinethene and maintained with open drop ether. The patient was supine. Her heart action was followed by a stethoscope which was strapped to her chest.

After 45 minutes of uneventful anesthesia, the attention of the anesthesiologist was attracted by what seemed to be repeated dropped beats. This was followed by totally irregular rhythm which persisted despite cessation of ether administration and full oxygenation. The beats were strong and the rate approximately 180. The blood pressure was 90/60 mm. Hg. After the arrhythmia had continued 10 minutes without significant change, it was decided to abandon the intended bone graft, and the wound was closed after obtaining a biopsy from the area of nonunion in the tibia. The patient was discharged. She was readmitted on Oct. 2, 1955, for study of her cardiac status and for further surgery.

An electrocardiogram taken at this time was within normal limits. In order to investigate sensitivity to the preoperative medication, the child was given the usual dose of morphine, Nembutal, and atropine, and another electrocardiogram was obtained. This was again normal.

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Since the consulting cardiologist suggested giving quinidine prophylactically, a 100 mg. trial dose of this drug was given without any resulting change in the electrocardiogram.

On Oct. 5, 1955, surgery was again undertaken. Premedication consisted of Nembutal 90 mg., atropine 0.4 mg., morphine 3.0 mg., and quinidine 100 mg. Ether was avoided. The anesthetic agents were thiopental and nitrous oxide with oxygen, under semiclosed circle technique. A delayed graft to the right tibia was performed, requiring 2 hours and 15 minutes. No cardiac disturbance occurred.

It was subsequently planned to take further grafts from a rib and the right tibia in order to replace the remaining defect in the left tibia. Since endotracheal anesthesia was indicated for this procedure, ether seemed preferable for this small child. On Nov. 4, 1955, with preoperative medication of Nembutal 90 mg., atropine 0.4 mg., morphine 3.0 mg., and quinidine 100 mg., the child was brought to the operating room once more. Before induction her pulse was 90 per minute, and her blood pressure 100/64 mm. Hg. Anesthesia was started using 3 L. of nitrous oxide and 1 L. of oxygen per minute, with semiclosed technique. Induction was smooth and uneventful, and ether was added gradually. Within 7 minutes after ether was started, an arrhythmia developed, followed by a marked tachycardia (pulse rate 190). Ether was stopped and 100 per cent oxygen was administered, with return of normal rhythm within 2 minutes. The blood pressure at this time was 100/70 mm. Hg. Another attempt was made to use ether, but within a few minutes the abnormal cardiac rhythm recurred. An electrocardiogram was taken at this time (Fig. 1) and revealed nodal tachycardia changing to auriculoventricular dissociation with interference beats. The operation was cancelled and 100 per cent oxygen again administered, with return to normal rhythm. However, the pulse remained rapid for 30 minutes.

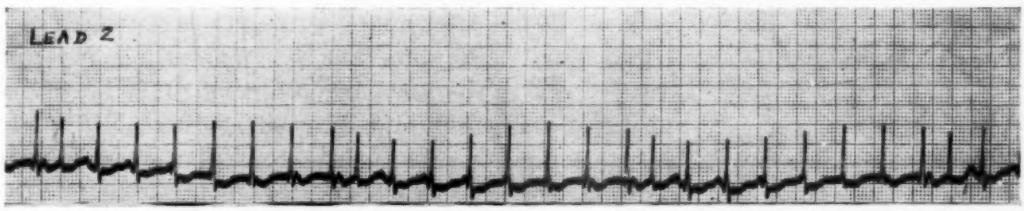

Fig. 1.—Abnormal rhythm (auriculoventricular dissociation with interference beats) which occurred repeatedly during ether anesthesia.

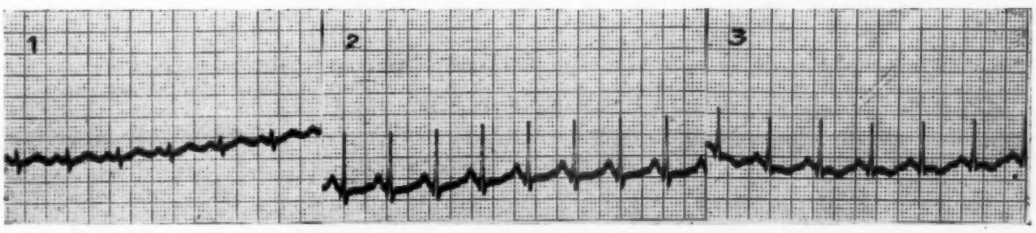

Fig. 2.—Normal electrocardiogram. Leads 1, 2, and 3 in same patient during thiopental, nitrous oxide, oxygen anesthesia.

On Nov. 9, 1955, under thiopental, nitrous oxide, oxygen anesthesia, a 4 hour procedure was performed without any detectable cardiac abnormality demonstrable by electrocardiogram (Fig. 2).

Inasmuch as this child had developed cardiac irregularity on repeated administrations of ether, it seemed highly advisable to look for an underlying cause, either in the heart itself, or in an associated disease process which would be manifested by cardiac arrhythmia. A cardiologist

was consulted to re-examine the heart. Physical examination again showed normal heart sounds, and no murmur, enlargement, or other evidence of organic heart disease. X-ray and fluoroscopy of the heart and chest showed no abnormalities. Sedimentation rate showed values of 30 uncorrected, and 20 corrected—wholly within normal limits. Hematocrit was 38 per cent. Antistreptolysin titer was reported as less than 50 units. These studies seemed adequate to preclude the presence of organic heart disease.

Since the biopsy taken at the time of the first bone graft proved to be neurofibroma, an associated pheochromocytoma with abnormal epinephrine release was considered. Accordingly, cold pressor and histamine tests were performed, but were negative. An intravenous pyelogram showed the kidneys and ureters to be normal. These results were taken as adequate evidence to rule out pheochromocytoma.

In order to investigate possible sensitivity to ether, patch tests were carried out. There was no abnormal reaction of the skin to ether. It was felt that a positive test would be good evidence for ether sensitivity; on the other hand, the fact that the skin test was negative does not exclude this possibility, since it is well known that many allergic persons do not show positive skin tests to allergens to which they are sensitive.

DISCUSSION

The significance of the particular arrhythmia encountered here deserves consideration. Many fleeting cardiac irregularities may be met during anesthesia and surgery without attracting more than passing interest. However, the development of atrioventricular dissociation is somewhat rare as a complication of anesthesia. According to Bellet,[10] the most common causes of atrioventricular dissociation are digitalis and occasionally quinidine toxicity, rheumatic myocarditis, and coronary artery disease. Prior to the first appearance of the arrhythmia this child had never received digitalis or quinidine, and her age certainly made coronary disease improbable. Rheumatic myocarditis could be a reasonable cause, but was ruled out by studies already described.

A vagal effect seemed unlikely as a cause of the arrhythmias, since tachycardia was a prominent feature. In this case, after a normal sinus rhythm of 90 at the beginning of induction, the rate rose to 200 with a nodal rhythm. On two occasions with rectal thiopental, nitrous oxide, oxygen anesthesia, there was no cardiac disturbance; and when ether was administered on two separate occasions by different techniques, a persistent arrhythmia developed. It appears that ether was the only agent which produced these abnormalities, and that the effect was directly on the heart, rather than being the result of vagal stimulation.

Hypoxia may produce cardiac irritability and arrhythmias but appeared improbable as the underlying factor here. A normal ventilation was maintained with good oxygenation at all times.

It was noted earlier that premedication and quinidine were eliminated as etiological factors on evidence of normal electrocardiograms. Having completed the procedures outlined above, it was felt that other possible factors such as vagal reflex, hypoxia, and pheochromocytoma had been excluded to our satisfaction. Although not proved to be the cause, sensitivity to ether appears to be the probable origin of the cardiac disturbances encountered in this case. We are left with the bare fact that on repeated exposure to ether anesthesia, this child showed definite cardiac arrhythmia. This might be called "sensitivity" to ether, except for the fact that the term has been used previously to describe

patients who showed cutaneous wheals and edema. More properly, the reaction of the child presented here might be termed increased cardiac irritability under ether.

SUMMARY

A study is presented of a 6-year-old girl who repeatedly developed marked cardiac arrhythmia during ether anesthesia. Organic heart disease, sensitivity to supplementary agents, pheochromocytoma, hypoxia, and vagal hyperactivity were eliminated as underlying factors. Increased cardiac irritability under ether anesthesia appears to be the most probable cause of the disturbances noted.

Appreciation for advice and suggestions is extended to Dr. Alexander Nadas, Cardiologist, The Children's Medical Center.

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WOLFF-PARKINSON-WHITE COMPLEXES ALTERNATING WITH LEFT BUNDLE BRANCH BLOCK

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MANY examples of Wolff-Parkinson-White complexes alternating with normally conducted beats have been published.[1-4] Also, Wolff-Parkinson-White complexes associated with various forms of heart block, such as complete heart block,[5] and two-to-one heart block,[2] have appeared in the literature, but as yet no instance of such complexes alternating with left bundle branch block has been published. It is the purpose of this case report to record for the first time such an unusual combination, in the hope that it may shed some light on the better understanding of the mechanism underlying the Wolff-Parkinson-White syndrome.

Table I. Analysis of Electrocardiograms

	Oct. 14, 1952		Oct. 23, 1952
	WPW complexes	LBBB complexes	
Heart rate	104/min.	104/min.	86/min.
P-P interval	0.57 sec.	0.58 sec.	0.70 sec.
P-R interval	0.10 sec.	0.14 sec.	0.13 sec.
QRS complex	0.15 sec.	0.16 sec.	0.14 sec.
P-J interval	0.25 sec.	0.30 sec.	0.27 sec.
"Electrical position"	vertical	horizontal	horizontal
"Transition zone"	V_3–V_4	V_4–V_5	V_4–V_5

Figures represent mean, calculated from all available complexes.

CASE REPORT

The patient, Mrs. J. C., aged 37 years, was first seen on Oct. 14, 1952. She had been suffering for several years from severe hypertensive heart disease punctuated by recurrent episodes of pulmonary edema. Left bundle branch block had been discovered 2 years earlier. On examina-

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tion she showed evidence of marked left ventricular enlargement, gallop rhythm, and a bigeminal heart action. Her blood pressure was 240/150 mm. Hg. There was no history suggestive of paroxysmal tachycardia, flutter, or fibrillation. She was not taking any drugs at the time. Electrocardiogram taken that day showed the unusual tracing of Wolff-Parkinson-White complexes alternating with left bundle branch block. On all subsequent occasions the electrocardiogram showed the usual pattern of left bundle branch block. The patient was treated with parenteral hexamethonium bromide. She has kept very well and fully active during the ensuing 4½ years.

Electrocardiograms taken on Oct. 14, 1952 (Fig. 1) and on Oct. 23, 1952 (Fig. 2) are analyzed in Table I.

DISCUSSION

Isolated case reports of the electrocardiographic syndrome of "short P-R interval with prolonged QRS complexes" were recorded by Wilson[6] in 1915, and by others, but the classical paper on the subject was published by Wolff, Parkinson, and White in 1930.[7] This represented a remarkable piece of collaboration by cardiologists from Boston and London, who did not meet personally until 24 years after the appearance of their now famous article. Current theories on the genesis of this unusual electrocardiographic pattern were summarized by Hunter and associates[8] in 1940, and further comprehensive reviews were published by Öhnell,[9] Prinzmetal and associates,[10] and Wolff.[11] Apart from the purely descriptive term "short P-R interval with prolonged QRS complexes," the Wolff-Parkinson-White syndrome has been referred to as the "pre-excitation syndrome," "aberrant atrioventricular conduction," "Bundle of Kent syndrome," and "accelerated conduction syndrome."

According to the classical concept, this condition occurs in healthy young individuals, whose only awareness of an anomaly depends on the frequent occurrence of attacks of paroxysmal tachycardia, commonly precipitated by effort. It has been estimated that approximately 5 per cent of bundle branch block electrocardiograms are due to this syndrome, and similarly that 5 per cent of patients subject to attacks of paroxysmal tachycardia show the Wolff-Parkinson-White syndrome.[8]

Until some 5 years ago, the most generally accepted theory postulated the existence of an accessory atrioventricular conducting bundle, the bundle of Kent. This would result in premature excitation of one ventricle, commonly the right, possibly resulting in a fusion beat, the impulse utilizing both anomalous and normal conducting systems. In recent years the complicated nature of this aberrant atrioventricular conduction has become apparent from the description of Wolff-Parkinson-White complexes occurring in various forms of heart disease, such as congenital heart disease, coarctation of the aorta,[12] hypertensive heart disease,[13] and ischemic heart disease,[2] as well as following the administration of cardiac drugs,[14] but especially from the report by Kossmann and associates[15] of the appearance of Wolff-Parkinson-White complexes during right heart catheterization, suggesting the role of direct endocardial stimulation in the production of this electrocardiographic pattern. Experimental studies by Prinzmetal and associates[10] led to the claim that the cause of the Wolff-Parkinson-White syndrome was some abnormality in the atrioventricular node with accelerated conduction through part of it, leading to premature excitation of one ventricle.

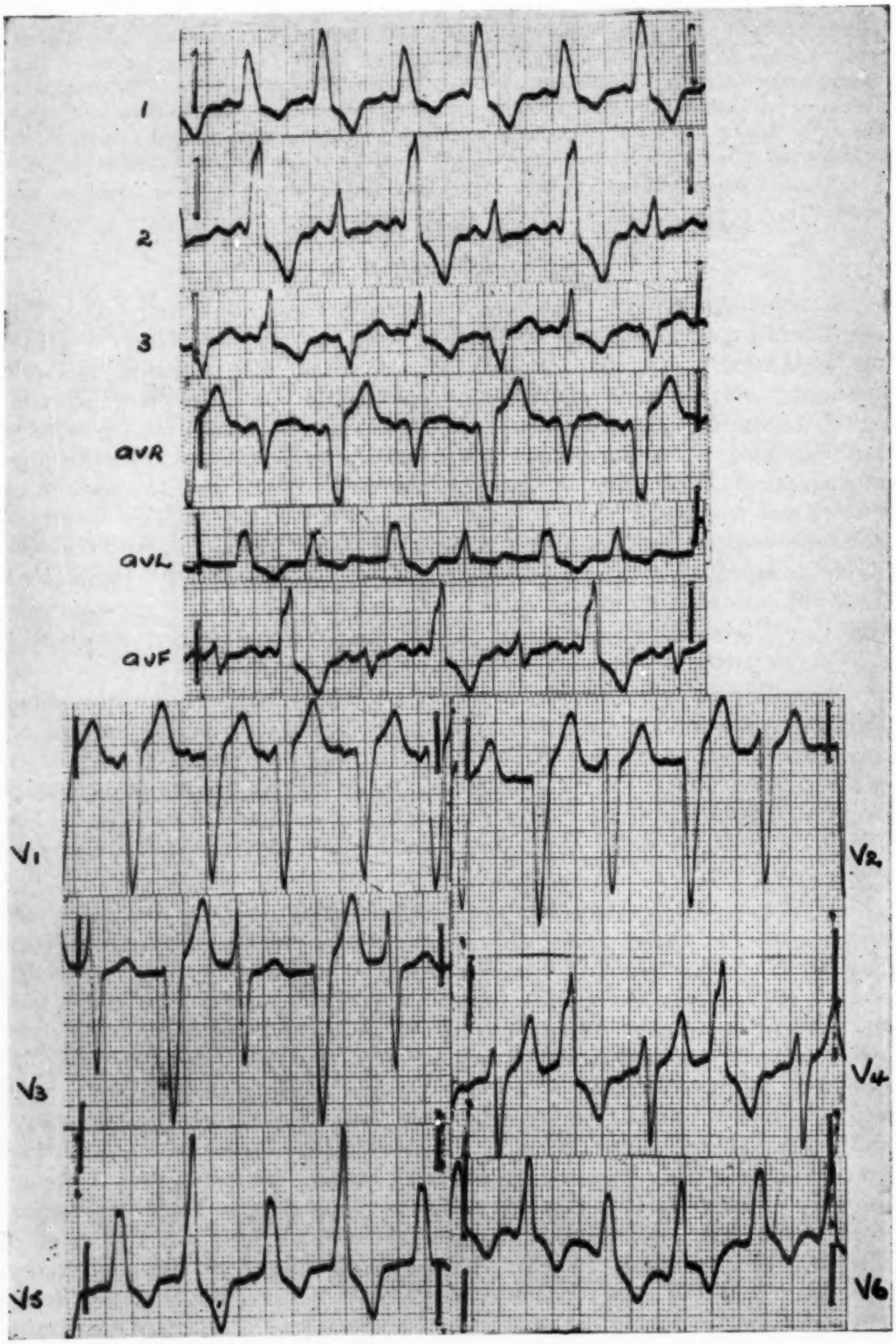

Fig. 1.—ECG taken on Oct. 14, 1952, showing WPW complexes alternating with LBBB complexes.

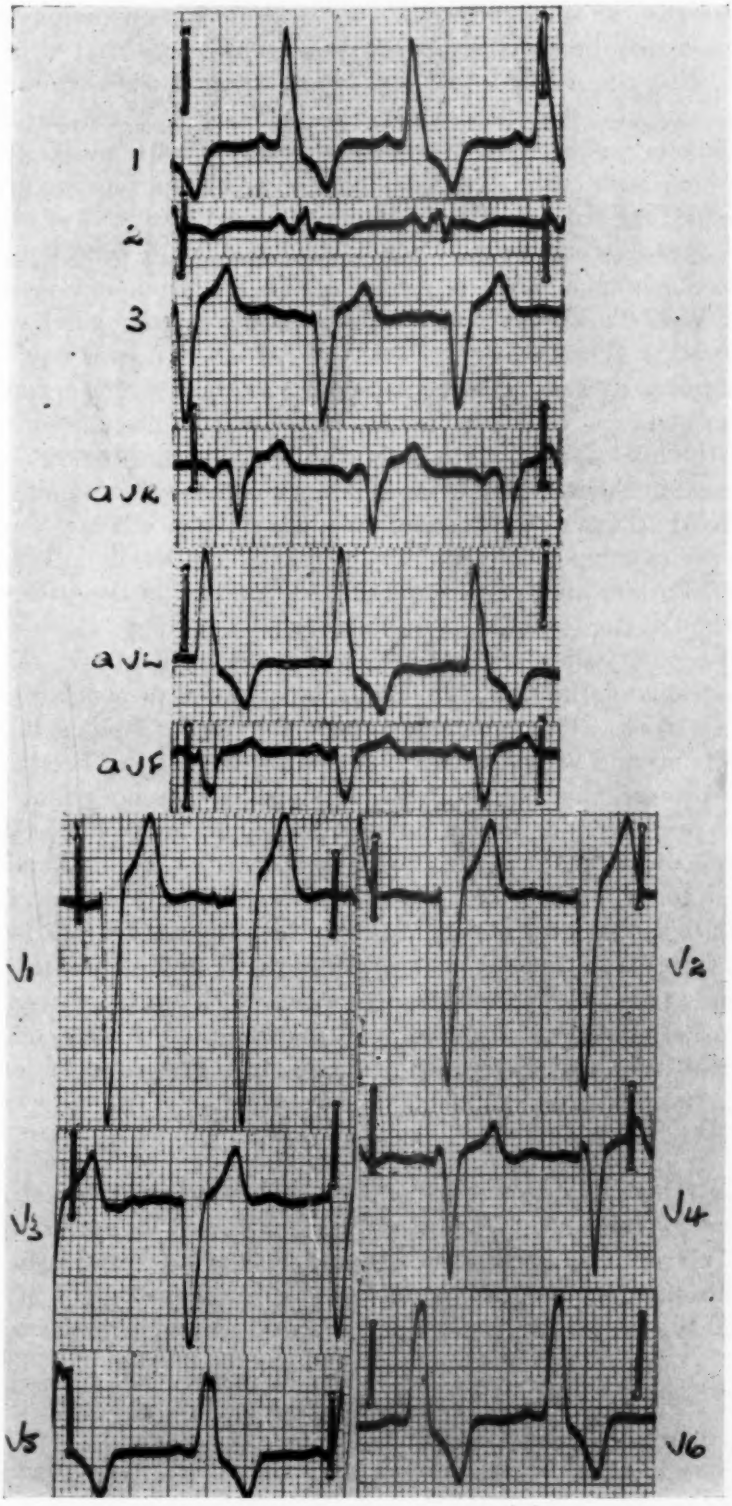

Fig. 2.—Electrocardiogram taken on Oct. 23, 1952, showing left bundle branch block. All subsequent electrocardiograms showed identical pattern.

It has been known since the original publication that anomalous atrioventricular conduction may be an intermittent phenomenon and that either spontaneously or following the use of nodal depressant drugs, such as quinidine or procaine amide, normal conduction may be re-established. Wolff-Parkinson-White complexes may occur as single beats or alternating with normally conducted impulses. Many such cases have been published without adding greatly to the understanding of the condition.

In this paper the occurrence of Wolff-Parkinson-White complexes alternating with left bundle branch block is recorded. In all previous papers describing intermittent Wolff-Parkinson-White complexes it was stressed that the sum of the P-R interval and the QRS complexes, the P-J interval, was equal in the normally and abnormally conducted beats. This fact was a strong argument in favor of some form of fusion beat with accessory as well as normal conduction contributing to the final pattern. However, in the electrocardiogram now published the P-J interval in the left bundle branch block complexes in significantly longer than the Wolff-Parkinson-White complexes, the difference being that of the P-R intervals of the two types of complexes. In both the left bundle branch block and the Wolff-Parkinson-White complexes the duration of the QRS complexes is the same although the form differs appreciably.

Since the observation of the alternation described above, all subsequent electrocardiograms of the patient merely revealed the presence of a stable left bundle branch block. Thus, the opportunity for further studies, both regarding the effect of drugs and hemodynamics, has unfortunately not been available. It is believed, however, that the observation is interesting enough, as a previously not reported phenomenon, to warrant putting on record. The possibility that Fig. 1 may represent ventricular extrasystoles occurring late in diastole, and thus representing a form of pulsus bigeminus, has been carefully considered. It seems unlikely that this is the true explanation for the following reasons: (1) The P-P intervals measured from the commencement of the P waves are identical throughout the tracing. (2) In all the subsequent years not a single extrasystole of similar configuration has veen observed. (3) No digitalis, likely to cause pulsus bigeminus, had been administered to the patient at the time the electrocardiogram of Fig. 1 was recorded.

SUMMARY

The case report of a hypertensive patient showing in the elcetrocardiogram Wolff-Parkinson-White complexes alternating with left bundle branch block is recorded. This type of alternation has apparently not previously been recognized and this electrocardiogram is published in the hope that it may aid in the elucidation of the mechanism underlying aberrant atrioventricular conduction.

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Review

CARDIOGENIC SHOCK

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CARDIOGENIC shock may be described as a breakdown of the circulation resulting from impairment of the function of the heart and characterized typically by severe hypotension, low pulse pressure, oliguria, cold clammy skin, and dulling of the sensorium.

HISTORICAL BACKGROUND

Although the picture of circulatory failure as we know it was recognized as early as the sixteenth century by men like Ambroise Paré,[1] the term "shock" was used first by a French surgeon named Le Dran[2] in 1743, to describe a deathlike state seen after trauma. James Latta[3] in 1795, first used the term to describe a moribund condition largely thought to be the result of inflammation. The term appeared more and more often thereafter to indicate severe circulatory failure in a variety of traumatic and nontraumatic diseases. Harrison[4] in 1935, and Blalock[5] in 1940, classified shock in four groups: oligemic, neurogenic, vasogenic, and cardiogenic. Since then the term cardiogenic shock has been reserved for severe circulatory failure resulting from diseases of the heart, such as myocardial infarction, severe tachycardia, terminal congestive heart failure, cardiac tamponade, dissecting aortic aneurysms, etc. Fishberg and associates[6] in 1934, after studying shock following myocardial infarction, concluded that both heart failure and peripheral circulatory failure were involved in the mechanism. Fishberg[7] later reversed his opinion and agreed with Boyer,[8] who in 1944, wrote a treatise in which he decided that the shock was due entirely to failure of the cardiac output. Boyer[9] reiterated this opinion as late as 1955. Wiggers,[10] in 1947, was the first to emphasize the role of failure of the heart in all forms of shock. Measurement of the cardiac output after myocardial infarction in man was reported by Grishman and Master,[11] in 1941, and was found to be diminished. The first measurement of cardiac output in man after myocardial infarction with shock was reported by Freis and associates[12] in 1952. Here again it was found decreased, but there was no consistent relationship between the decrease in cardiac output and the occurrence of shock. Thus, the mechanism of shock following myocardial infarction is still disputed.

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NONCORONARY CARDIOGENIC SHOCK

The most common cause of cardiogenic shock is acute myocardial infarction. Shock, however, may be found also in association with many other diseases which produce cardiac abnormalities.

When shock occurs with cardiac tamponade, the basic abnormality in hemodynamics is marked interference with cardiac filling which leads to a falling cardiac output, blood and pulse pressure, and to a rising venous pressure.[13] Cardiac tamponade and shock may be caused by hemorrhage into the pericardial cavity due to trauma, anticoagulants, or rupture of a dissecting aortic aneurysm or myocardial infarct. Other causes of cardiac tamponade and shock include rheumatic,[13] bacterial,[13] and uremic[14] pericarditis. Shock has been described also in association with primary idiopathic pericarditis when severe pain is present,[15] leading to confusion with coronary shock. Significant subepicardial myocardial damage is seen in both clinical and experimental severe acute pericarditis.[16,17,18] The degree to which these myocardial changes contribute to shock, if at all, is still unsettled.

The contribution of the myocardium to the development of shock is most clearly evident when it occurs in the terminal phases of severe congestive heart failure.[19] The primary change is a marked decrease in cardiac ouput which leads, in turn, to intense but ineffectual vasoconstriction. In contrast, the shock state which may occur with beriberi cardiovascular disease has been attributed to a combination of heart failure and vasomotor collapse manifested by marked arteriolar dilatation.[20] Shock, as well as sudden death, may occur in the presence of myocarditis,[21,22] which may be part of the picture of acute infectious disease or may occur in isolated form.[23] While myocarditis is frequent in diphtheria,[24] shock is usually a terminal event and has been attributed to failure of the peripheral vasomotor mechanism,[25] although the associated myocarditis may play a contributory role.[21] Changes interpreted as myocarditis have been reported in from 40 to 90 per cent of patients dying from poliomyelitis.[26] Shock, however, has been limited essentially to patients with bulbar involvement and is thought to be due primarily to damage to the vasomotor center,[26] with the role of the myocarditis in doubt.[27]

Shock has been observed in association with malaria,[28] typhoid fever,[29] scarlet fever,[30] and in other severe infections with and without septicemia.[31] In these instances, it is felt that shock is probably not due to the presence of myocarditis but rather to toxins acting on peripheral vessels or the medullary centers, producing a fall in total peripheral resistance and diminution in venous return.[31,32]

Acute heart failure and a shocklike state may follow such cardiac catastrophes as septal perforation or papillary muscle rupture during acute myocardial infarction, or rupture of valve cusps or chordae tendineae with trauma or bacterial endocarditis.[13] Other cardiac abnormalities which may cause shock due to acute heart failure, often with intense vasoconstriction, are those which produce obstruction to blood flow, as observed with a ball-valve thrombus, severe mitral or aortic stenosis, or with myxoma of the heart.[33,34]

Dissecting aortic aneurysms may produce shock or a shocklike picture which may be mistaken for coronary shock. Galbraith and Norman[35] noted the clinical

appearance of shock even when the blood pressure was not lowered. David and associates[36] observed the presence of shock in 6 out of 17 patients with aortic dissecting aneurysm, usually in association with severe pain. Sampson[37] stated that hypotension does not occur prior to rupture of the aneurysm. Zendel and Paulin[38] described a patient who entered into deep shock and who required levarterenol (Levophed) for 12 days in order to maintain the blood pressure, until death suddenly occurred from rupture of a dissecting aneurysm of the arch of the aorta. We observed a 64-year-old white man who entered into severe shock following the occurrence of severe crushing substernal pain. The blood pressure was not obtainable by auscultation; the systolic blood pressure was 50 mm. Hg by palpation. Electrocardiograms were normal. The shock was intractable to morphine, large doses of Levophed, and to intra-arterial blood transfusion, and the patient died 18 hours after entry. The autopsy revealed a blood clot, measuring 8 × 4 × 2.5 cm., between the media and adventitia of the ascending aorta. No blood was found in either pleural cavity, and only 45 c.c. of blood was present in the pericardial cavity. The coronary ostia and vessels were patent and no myocardial infarction was present. We also saw irreversible shock following the inadvertent dilatation of the root of the aorta in a patient in whom the surgeon was attempting to dilate a stenosed aortic valve. No hemorrhage was found at autopsy. It is possible that this type of shock may be due to intense stimulation of the aortic baroreceptors. A similar mechanism has been suggested as a factor in the hypotension occurring during thoracic surgical operations.[39] A comparable form of neurogenic shock has been produced experimentally by prolonged stimulation of the carotid sinus in anesthetized dogs.[40]

Severe hypotension may be produced by some drugs commonly used to treat cardiovascular disease. Narcotics such as morphine, while usually very valuable in the treatment of shock due to or accompanied by severe pain, may at times produce severe postural hypotension resembling shock.[41] Pronestyl, if given intravenously at a rapid rate, may produce severe lowering of blood pressure through its vasodilating effect. The hypotensive effect of the veratrum alkaloids is mediated not only via the brain and carotid receptors, but also by the vagal stimulation involved in the Jarisch-Bezold reflex, leading to bradycardia and peripheral vasodilation. It was shown by Dawes[42] that this effect can be produced in a few seconds by direct injection of the veratrum alkaloids into the left coronary artery (but not into the right), indicating that cardiac receptors are involved in this reflex. Shock may be produced also by any of the ganglionic blocking agents, such as tetraethylammonium (Etamon), hexamethonium (Bistrium, Methium, etc.), pentolinium (Ansolysen) or chlorisondamine (Ecolid). These drugs block vasoconstrictor sympathetic impulses and produce peripheral vasodilation, venous pooling, and, hence, a decrease in cardiac output.[43]

Shock has been noted often in the presence of acute cor pulmonale due to pulmonary emboli.[13,44] These are frequently massive enough to produce at least partial obstruction of a major pulmonary artery. When shock occurs in the presence of smaller pulmonary emboli, the best evidence indicates that a vagal reflex is responsible,[37,45] since the experimental production of such shock can be

prevented by blocking the vagal pathways.[46] The hemodynamic changes observed in this type of experimental acute cor pulmonale include a decrease in cardiac output and an increase in central venous pressure and pulmonary artery pressure. Recently, clinical confirmation of these experimental observations was supplied by Selzer and Bradley,[47] who reported a patient in whom pulmonary embolism occurred during cardiac catheterization. Schafer and associates[48] reported 3 patients with essential pulmonary hypertension who died shortly after cardiac catheterization, shock being due either to stimulation of vagal receptors in the pulmonary arteries or to acute right heart failure.

Both supraventricular and ventricular tachycardias may cause severe hypotension and shock. The shortened diastolic interval leads to decreased diastolic ventricular filling and a drop in cardiac output.[13] In most of these instances, shock occurs in the presence of underlying heart disease, but not always. Thus, Finkelstein and associates[49] described 6 cases of auricular flutter with 1:1 ventricular response. The blood pressure was unobtainable in 5 of these patients. The only death occurred in a patient who maintained a ventricular rate of nearly 300 for 4 days, but in whom the heart was otherwise normal. Wolff[50] reported 15 cases of shock from paroxysmal ectopic tachycardia; 4 of these had no evidence of heart disease. Sturnick and associates[51] collected 15 cases of ectopic tachycardia with the clinical appearance of shock; 1 patient had no evident heart disease. It is felt by most authors that shock does not occur with heart rates slower than 180.[52] As might be expected, shock occurs more readily the more severe the underlying heart disease and the longer the duration of the tachycardia. Heart failure may or may not be present. Thus, in the series reported by Wolff[50] only 4 of the 15 patients had associated congestive heart failure.

Wiggers[10] introduced the concept that the heart participates in most forms of shock, including that which follows trauma or hemorrhage. In experimental hemorrhagic shock, if the hypotension is sufficiently prolonged, complete restoration of the blood volume will fail to relieve the shock. Cardiac output and stroke volume continue to decrease until death supervenes. Both anatomic and biochemical changes have been described in the heart following shock. Melcher and Walcott[53] found that any type of prolonged shock in dogs was capable of producing infiltration of leukocytes and necrosis of heart muscle, presumably due to anoxia. Blumgart and associates[54] found that shock due to any cause could produce multiple myocardial infarcts in the absence of coronary occlusion. Pollak[55] reported 96 patients, of all ages, in whom hydropic swelling of the intimal endothelial cells of the coronary and other arteries was found in association with shock of various origins. These changes were not observed in a control series of patients in whom death was not associated with shock. Bing[56] demonstrated decreased coronary blood flow in shock, apparently produced by the decreased filling pressure. Opdyke and Foreman[57] found that both coronary blood flow and coronary vascular resistance decreased in hemorrhagic shock; adequate myocardial oxygenation was quickly restored if transfusion was given promptly. Edwards and associates[58] studied myocardial metabolism in experimental hemorrhagic shock and found that a metabolic break occurred between pyruvate and acetate in the glycogenolytic cycle, due to inhibition of cocarboxylase. Hackel

and Goodale[59] observed that the myocardial extraction of pyruvate was reduced in shock, as opposed to the findings in heart failure. LePage[60] described a decrease in adenosine diphosphate (ADP) in heart muscle when shock was present. Gellhorn and associates[61] found that, in shock, the movement of sodium across the cellular membrane was decreased by one half. Thus, the heart was shown to play not a passive but a vital role in severe shock of any origin; this fact must be strongly considered if irreversibility of shock is to be prevented.

EXPERIMENTAL BACKGROUND

For nearly a century the literature has chronicled the experiments of numerous investigators who have studied the pathophysiology of myocardial injury. The methods of producing myocardial necrosis have multiplied from the crude experiments of Panum,[62] in 1862, who injected wax and lamp black into the aorta, to the controlled myocardial injury produced by Taylor and his co-workers,[63] in 1951, with a hypothermal instrument cooled by expanding carbon dioxide. None of these methods, however, produced protracted cardiogenic shock. Samuelson,[64] in 1881, was the first to attempt coronary artery ligation. Since that time, single and multiple ligations of the coronary arteries to the atria, septa, and ventricles of both rabbits and dogs have resulted only in a slight drop in blood pressure,[65-70] or in ventricular fibrillation,[65,68,70-72] or occasionally in congestive heart failure.[65,68,72] In 1951, Kupfer[73] restudied the problem of circulatory failure after coronary artery ligation and stated that "The results indicate that up to 7 hours there is no evidence, on the basis of an analysis of cardiac output, blood volume, and pressure pulses, that circulatory failure of peripheral origin supervenes in dogs after ligation of a major coronary branch."

Chemical, traumatic, hyperthermic, and hypothermic methods have been used to produce myocardial destruction[63] but neither heart failure nor shock has occurred. These methods include such experiments as those of Starr and associates,[74] who burned the entire right ventricle without producing a rise in venous pressure, and the experiments of Eppinger and Rothberger[75] who froze the heart with ethyl chloride. Occlusion of the coronary arteries by the introduction of emboli was first attempted in 1926, by Hamburger and associates,[76] who used Lycopodium spores. Herrmann and Decherd[77] adroitly introduced metallic mercury into the coronary ostia through a slit in the carotid artery. But it was Roos and Smith[78] who first made any approach to the production of coronary shock. They injected a 3 per cent starch suspension into the left ventricle of the open-chest dog while manually occluding the aorta. They observed acute heart failure ensuing in 15 to 35 minutes, and although the animals lived only 10 minutes longer, the blood pressures of some animals fell to low levels before death occurred. Meyers and associates[79] reported blood pressure falls in 5 of 10 animals following closed-chest injection of the myocardium (chiefly septum) with necrotizing zinc hydroxide. These results are difficult to evaluate (no electrocardiographic data are recorded) in spite of the probability that severe arrhythmias usually result from septal infarction and in themselves lower blood pressure.

The literature contains contradictory statements in regard to the occurrence of "shock" after myocardial injury. Drops in mean arterial pressure (MAP) up to

15 per cent of the control values, and lasting up to 10 minutes, may occur occasionally after coronary artery ligation.[70,80-82] This, however, is transient hypotension and not shock. As has been indicated, the results of innumerable investigators have shown that coronary artery ligation or other methods of producing severe myocardial injury have not produced severe protracted shock. This was first achieved by the coronary embolism technique to be described below. Using this technique it was found necessary to establish strict criteria for the occurrence of shock.[83] Experimentation showed that, when the MAP was reduced 30 per cent from the resting level and remained down with no tendency to rise for at least 30 minutes, the animal would eventually die unless treated. Animals which developed arrhythmias within the 30 minute period were excluded. In future work, the subject will be greatly clarified if such criteria for severe shock are carefully observed.

EXPERIMENTAL CORONARY SHOCK

Since 1951, our group has been conducting experiments using a catheter technique developed in our laboratory.[83] Simply, the technique consists of introducing a specially devised double lumen metal catheter into the left carotid artery of the dog after making a small incision in the neck. The catheter is threaded down to the mouths of the coronary arteries, whereupon a strong rubber balloon is inflated until aortic blood flow is completely occluded. At this point, plastic microspheres ranging in size from 125 to 450 micra are injected into the aorta and are pumped by the strongly beating ventricle into the coronary arteries of both sides. The spheres at injection are suspended in 15 per cent acacia solution, and it has been found that about 50 per cent of the injected spheres enter the coronary arteries during the occlusion period of 15 seconds. Acacia alone, when warmed to body temperature, will not cause any fall in blood pressure, nor will repeated inflation of the balloon do so. Spheres which enter the systemic circulation after the balloon is deflated and after flow is resumed lodge largely in the skin and muscles. A small per cent are found in other organs, such as the kidney or brain, but these do little harm and cause no change in the control blood pressure. Thus, the technique of closed-chest coronary embolization will cause shock (see criteria in preceding section) in about one sixth of the animals injected.[83] By avoiding thoracotomy the factor of hemorrhage is eliminated completely and trauma is minimal.

With this method, several hundred experiments have now been performed in an effort to study blood volume changes, peripheral and central venous pressures, pulmonary artery, femoral artery, intraventricular and left atrial pressures, oxygen saturation, cardiac outputs (CO) and stroke volumes, total peripheral resistances (TPR), and observations on the activity of the vagus and sympathetic nerves as well as the posterior roots of the upper thoracic nerves.[83,92,127] It was desired (1) to determine the presence of hypovolemia by studying the blood volume changes, (2) to discover what relation, if any, the amount of heart damage bears to the occurrence of shock, (3) to test whether heart failure was necessary for the shock state, (4) to see if the Jarisch-Bezold reflex was an important part of the mechanism, and (5) to find out what role the nervous system played.

It was found early that some reduction in blood volume occurred after prolonged severe shock, the maximum reduction being −16 per cent; and that the greater loss of plasma from the circulating blood accounted for the observed hemoconcentration. However, it is established that approximately 40 per cent reduction in blood volume is necessary for the occurrence of hypovolemic shock.[84-86] Moreover, it was found that maintenance of the blood volume with blood or plasma did not prevent or ameliorate the shock. Finally, shock occurred shortly after the introduction of spheres, while the reduction in blood volume required several hours. It was concluded that reduction in blood volume was not an important factor in the production of shock.

Many methods were used in an effort to decide whether or not shock occurred simply as a function of the decline in cardiac output which followed progressive coronary occlusion and myocardial infarction. The work of previous investigators cited above is strong evidence that shock

is not due solely to the amount of damaged heart muscle. It was not possible to demonstrate any correlation between the occurrence of shock and the number of spheres per gram of digested heart muscle, the amount of infarction estimated grossly and on microscopic section,[83] or gross disturbances of cardiac function as observed with color movies of the beating heart. In badly shocked animals, it has been possible by inflating the intra-aortic balloon to raise the intraventricular pressure to levels as high as 200 mm. Hg, thus demonstrating the reserve contractile force still available. Hemodynamic measurements were then carried out as illustrated below.[127] In these experiments, the animals were divided into two groups, (a) those damaged repeatedly until death ensued but in which no significant fall in blood pressure occurred, and (b) those damaged until a shock level of blood pressure was obtained. Fig. 1 shows an example of the first group (a). Note that the fall in CO is severe, approximately 50 per cent of the control value, but that the MAP is well maintained by a rise in TPR of 100 per cent. Fig. 2 is an example of the second group (b). The CO is reduced but no more severely than in the first group (a), while the MAP is 60 per cent of the resting level. In these animals, the TPR shows no tendency to compensate for the falling CO and the blood pressure cannot be maintained. Yet, the injury sustained by the myocardium in terms of stroke volume or cardiac output is not so great as in the animals which remain normotensive.

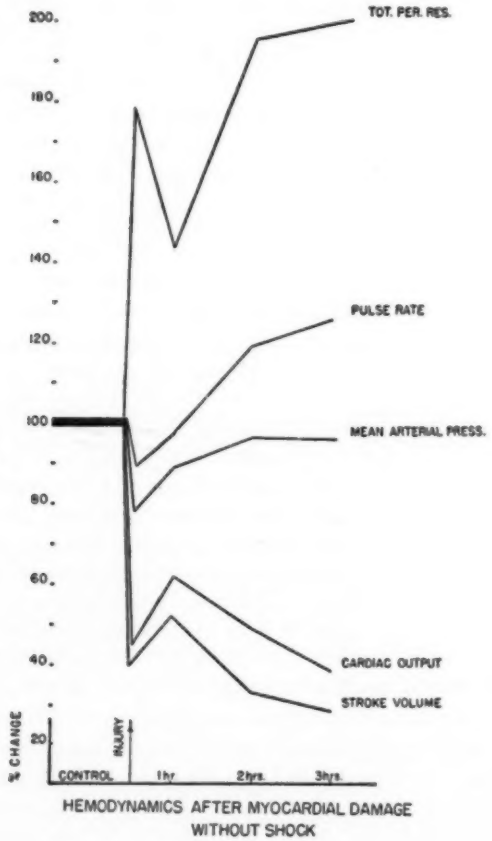

Fig. 1.

It has been demonstrated also that shock may occur in the absence of congestive heart failure: that is, in the absence of a rise in central venous pressure, in pulmonary artery pressure, in left atrial pressure or left ventricular diastolic pressure, and in the absence of severe congestion of the viscera. Fig. 3 is a typical example of such central measurements. Note the falling stroke output of the left ventricle without any rise of the diastolic pressure. Fig. 4 demonstrates that shock

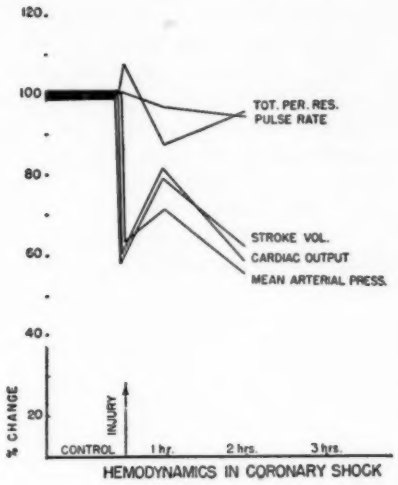
120.
100
80.
60.
40.
TOT. PER. RES.
PULSE RATE
STROKE VOL.
CARDIAC OUTPUT
MEAN ARTERIAL PRESS.
% CHANGE
20
INJURY
CONTROL
1 hr.
2 hrs.
3 hrs.
HEMODYNAMICS IN CORONARY SHOCK

Fig. 2.

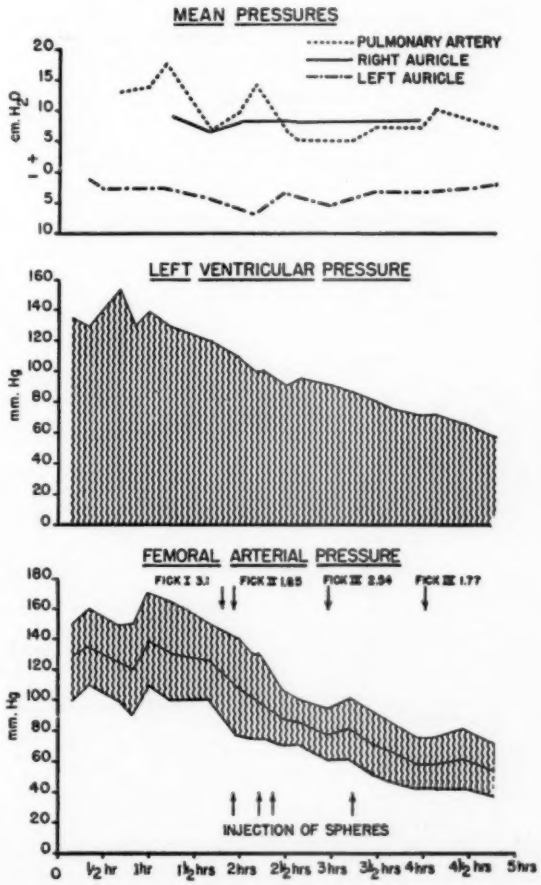
MEAN PRESSURES
PULMONARY ARTERY
RIGHT AURICLE
LEFT AURICLE
cm. H2O
LEFT VENTRICULAR PRESSURE
mm. Hg
FEMORAL ARTERIAL PRESSURE
FICK I 3.1
FICK II 1.85
FICK III 2.54
FICK III 1.77
INJECTION OF SPHERES
0
½ hr
1hr
1½hrs
2hrs
2½hrs
3hrs
3½hrs
4hrs
4½hrs
5hrs

Fig. 3.

is present long before there is any rise in central venous pressure. As time passes there is a trend upward in the central venous pressure and in the blood volume (in surviving animals) so that heart failure may be added to shock, but there is no evidence in these experiments that heart failure is at all necessary for the production of severe shock, and in many instances it is completely absent. A moderate rise in peripheral venous pressure is not a reliable criterion of heart failure because of the associated venoconstriction which often is present.

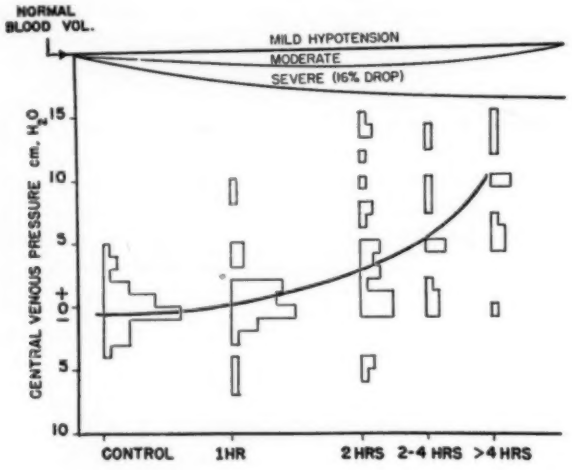

Fig. 4.

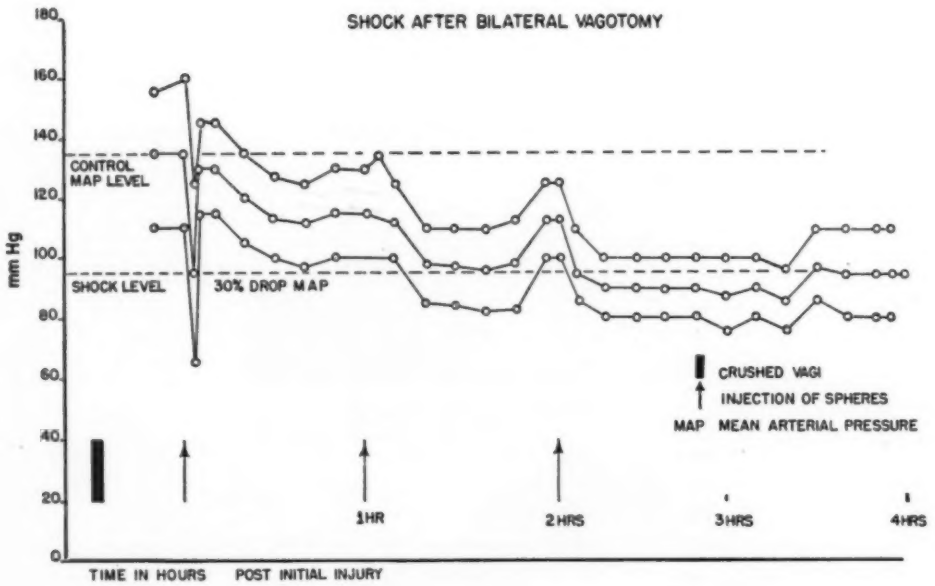

Fig. 5.

That the classic Jarisch-Bezold reflex, i.e., hypotension and bradycardia mediated through reflex vagal action, is not necessary for this form of shock is amply shown in Fig. 5, in which shock has occurred after bilateral vagotomy. Further, bilateral vagal section does not relieve the shocked state.

Finally, since the mechanism of experimental coronary shock seemed to hinge on some interference with the usual compensatory vasoconstrictor reflexes, a study of the role of the nervous system was undertaken. It was postulated that heart injury in some animals set up afferent impulses which in some way prevented the usual sympathetic response.[127] Since the pathway through the vagus was eliminated, only the afferent sympathetic fibers in the thoracic cardiac

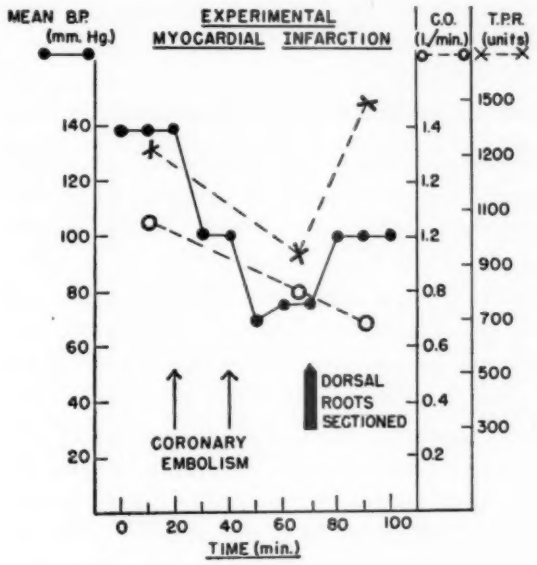

Fig. 6.

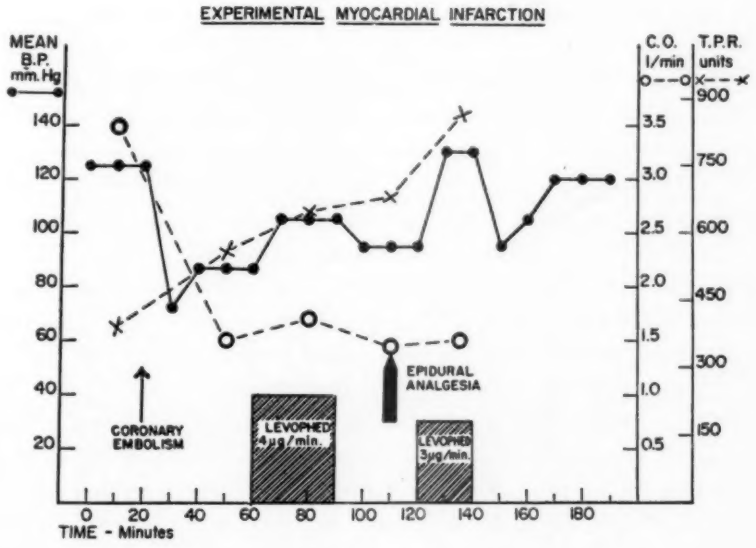

Fig. 7.

nerves and upper thoracic and lower cervical dorsal roots remained. It seemed reasonable that blockage of these pathways might permit increased peripheral vasoconstriction. Fig. 6 illustrates this type of experiment where section of the posterior dorsal roots at the level of C_7 to T_6 resulted in a rise in TPR and MAP without alteration in CO. Fig. 7 shows how an animal that had had

maximal response to Levophed showed an additional rise in TPR with less Levophed, after epidural block with procaine anesthetized the upper sympathetic afferent pathways. It remained to test directly whether or not sympathetic activity was altered in coronary shock. An electronic pickup and amplification of nerve action potentials was used for accurate counting of sympathetic efferent activity of the greater splanchnic nerve (unpublished data). No increase (and often a decrease) in the number of action potentials per unit time was demonstrated in the presence of coronary shock, whereas asphyxia or hemorrhagic shock were associated with marked increases in these impulses in the same animals.

CLINICAL CORONARY SHOCK: HEMODYNAMIC CHANGES

Hemodynamic studies in human coronary shock are scanty due to the difficulties inherent in measuring such changes in severely ill patients. Four groups of investigators have reported such studies.[12,87-89] As reported in a review of clinical coronary shock,[90] much of the data is limited by failure of the investigators to agree on uniform criteria for the syndrome. For example, severe coronary shock was diagnosed in the face of a MAP of 112.[87] In general, the cardiac output has been found to be very low, but equally low cardiac outputs were found in patients who had acute myocardial infarction without shock.[87] Of further significance is the fact that of the 14 reported cases of severe coronary shock (with CO data) (Table I) only 8 showed an increased TPR, while in the remaining 6 the TPR remained normal and failed to rise in the face of a low blood pressure and cardiac index. Fortunately, in 2 of these 14 cases, studies were conducted before and after a fall in blood pressure. Thus, in Case 1, although the MAP fell from 120 to 72, and the cardiac index from 3.4 to 2.4, the TPR did not increase; indeed it changed from 1,550 to 1,300. In Case 3, when the MAP changed from 88 to 73, the TPR changed from 2,350 to 2,100.

TABLE I. HEMODYNAMIC CHANGES IN CLINICAL CORONARY SHOCK

AUTHORS	YEAR	PATIENT NUMBER	MEAN ARTERIAL PRESSURE (MM. Hg)	CARDIAC INDEX (L./M.²/MIN.)	TOTAL**** PERIPHERAL RESISTANCE (DYNES SEC./CM.⁵)	H_2O VENOUS PRESSURE (MM. H_2O)
		1*	72	2.4	1,300	115
Freis et al.	1952	2	83	1.5	2,450	90
		3	73	1.5	2,100	140
		4	52	1.6	1,200	270
		5	58	1.9	1,280	88
Smith et al.	1954	6	54	1.3	1,360	176
		7	60	1.4	2,080	74
		8	84	1.5	2,480	81
		9	70	1.3	2,160	149
		10	77	0.8	3,900	220
Gilbert et al.	1954	11	54	0.8	3,400	65
		12	32	0.6	1,600	175
		13	90	**	1,432	***
Gammill et al.	1955	14	85	**	2,367	***

*Case 1.—Preshock values were: MAP = 120; CI = 3.4; TPR = 1,550.
**Only stroke volume reported: Patient 13 - 43 c.c., Patient 14 - 22 c.c.
***No data given.
****Average normal TPR values in these cases are 1,400.

The venous pressure in coronary shock may be normal or elevated (Table I) depending on the presence of venoconstriction, the duration of shock, and the superimposition of congestive heart failure. This correlates well with the findings in animal experiments.

Blood volume studies in patients with coronary shock[12,87,91] have shown that the blood volume may be decreased, normal, or increased. The variation in results is related to the duration of the shock, its severity, and the presence or absence of heart failure. Smith and associates,[87] in 1954, measured the blood volume in patients within 2 hours after the development of coronary shock; in these patients no reduction in blood volume was found. This conclusion is misleading, however, since it should be appreciated that fall in blood volume is a function of time, being maximal in 24 hours. A study done within 2 hours of the onset of shock is not likely to show much reduction. In shocked dogs there was only a 5 per cent reduction in blood volume during the first hour, but in 5 hours there was a 15 per cent reduction.[92] The study is significant, however, because it shows that shock existed at a time when there was no reduction in blood volume. If all factors are correlated, it is found that the alterations in blood volume are never great, but that the trend is downward as shock advances, but tends to increase after 24 hours, especially if heart failure supervenes (Fig. 4).

THERAPY OF CORONARY SHOCK

The treatment of noncoronary cardiogenic shock is directed to the specific etiologic agent (e.g., relief of cardiac tamponade, treatment of infection, abolition of ectopic tachycardia, etc.). The treatment of coronary shock to date has been largely empirical; further clarification is needed.

In the past decade the therapeutic approach to coronary shock has changed from one of nonspecific support to one of active intervention. The use of various drugs, vasopressor agents, infusions into arteries and veins, digitalization, and the like, have altered the mortality rate, but not always favorably. Any agent which is regarded as beneficial must reduce the natural mortality rate, and if the latter is to be assessed properly, criteria for the definition of severe coronary shock must be uniform. These criteria may be summarized as follows: (1) acute myocardial infarction proved by electrocardiogram or autopsy, (2) systolic blood pressure 80 mm. Hg or less (except in patients previously hypertensive where shock may rarely occur at slightly higher levels), (3) clinical signs of peripheral circulatory collapse, such as marked oliguria or anuria, pallor or cyanosis or both, marked sweating, cold skin, and dulled sensorium, and (4) absence of other causes for shock, such as hemorrhage, embolism, infection, acidosis, etc. For the evaluation of new therapy, two other criteria are needed: (a) no improvement in the shock state for ½ hour after relief of pain and administration of oxygen, and (b) survival of the patient for at least 1 hour after initiation of new therapy.

In a previous publication,[90] it was pointed out that the reported natural mortality rates bore an inverse relationship to the reported incidence of shock. Those authors who were less strict about criteria reported lower mortality rates because they were treating milder degrees of shock. However, when the same criteria for severe coronary shock were observed, the agreement about mortality

rates was surprisingly good. Approximately 1 patient out of 5 survives if nothing is done except to administer oxygen and relieve pain. A reduction in mortality rate from 80 to 60 per cent has been accomplished largely by the use of vasopressor agents. Any new agents for which efficacy is claimed must be capable of lowering the mortality rate below 60 per cent.

The prompt use of oxygen and the relief of pain with narcotics are the first steps in the management of coronary shock. Since it has been shown that with shock there is a delay in absorption from subcutaneous tissues,[93] it is wise to administer the narcotic intravenously. Morphine, Demerol, and Dilaudid, all are effective. The injection should be given slowly and overdosage avoided, since, if more narcotic is administered than is required to relieve pain, further depression of the blood pressure may ensue.[41]

The use of infusions and transfusions is now on the wane because their use has failed to lower the mortality rate. While an occasional patient may obtain a slight rise in blood pressure during intra-arterial transfusion, this is limited usually to the duration of the transfusion. Intravenous transfusions have served only to increase the mortality rate. Thus, in 59 reported cases in which intravenous transfusions were used, the over-all mortality rate was 90 per cent,[94-96] while in 310 patients in whom expectant treatment alone was used, the mortality rate was 80 per cent.[94,97-101] The death rate in 42 patients who were given intra-arterial transfusions was 81 per cent.[101-103] Since it was shown above that hypovolemia is either absent or slight in this form of shock, these results are not surprising.

There are in present use a number of vasopressor drugs varying in effectiveness (Table II). There is fairly good agreement that Levophed is the most potent and fastest acting of the vasopressor agents. Its disadvantage, however, is that it must be administered intravenously, and that infiltration of the tissues may produce a slough. For prolonged administration most physicians prefer to administer it through a polyethylene catheter inserted into an antecubital vein. It is well to start with a concentration of 8 mg. in a liter of 5 per cent glucose in water. The rate necessary to produce a significant pressor response, i.e., systolic blood pressure of 100 to 110 mm. Hg, is quickly determined. The concentration is then readjusted to permit maintenance of the blood pressure with the infusion flowing at the rate of 1 c.c. per minute. It has been found advisable to increase the concentration rather than the volume in order to avoid overloading the circulation. Concentrations above 24 mg. per liter rarely have been effective. Frequent measurements of the blood pressure are necessary to avoid overshoot. Should the Levophed solution infiltrate into the tissues, prompt injection of procaine into the area will usually prevent a slough. Recent reports indicate that the local infiltration of phentolamine (Regitine), with and without hyaluronidase, will also prevent Levophed sloughs.[104,105] It has been reported[106] that a decrease or abolition of sympathetic activity occurs regularly with infusions of pressor agents in experimental animals. A decrease in the number of efferent sympathetic impulses has been observed similarly in our laboratory animals during Levophed infusion. Consequently, as the patient improves and the blood pressure stabilizes, the rate of infusion should be decreased slowly, for sudden withdrawal will permit vasodilatation and a precipitous fall in blood pressure.

TABLE II. VASOPRESSOR DRUGS

NAME	INOTROPIC	PULSE	CORONARY	ROUTE	DOSE	COMMENT
Neo-Synephrine (phenylephrine)	None	Slows	None	Subc. I.M. I.V.	1–10 mg. 1–10 mg. (5 mg. q. 15 min.) 0.5 mg.	Useful in Par. Tachy. Not used in partial heart block
Vasoxyl (methoxamine)	None Cen. Ven. PR. +	Slows	None	I.M. I.V. infusion	10–15 mg. (q. 15 min.) 10 mg. 12.0 mg./100 c.c.	Useful in Par. Tachy. No tachyphylaxis
Wyamine (mephentermine)	Positive	None	Increased	I.M. I.V. infusion	15–35 mg. (15 min. delay) 5–20 mg. 1 mg./min.	Possible tachyphylaxis
Levophed (levarterenol)	Positive	May Slow	Increased	Infusion	4–8 mcg./min.	May cause slough
Aramine (metaraminol)	Positive	None	Increased	Subc. I.M. I.V.	2–10 mg. 2–10 mg. 3.0–20.0 mg./100 c.c.	 No slough No tachyphylaxis Prolonged action

Subc. = subcutaneously; I.M. = intramuscular; I.V. = intravenous; Cen. Ven. PR. = central venous pressure; Par. Tachy. = paroxysmal tachycardia.

It is important to recognize that a pressor response does not necessarily mean relief of shock. Of 131 reported cases,[90] 85 per cent exhibited a pressor response, but only 53 per cent were relieved of shock. The urinary output has been found to be a very sensitive index of shock. For this reason it is advisable to insert an indwelling urinary catheter and measure the output of urine. We have found that relief of shock is usually associated with a urine flow exceeding ½ c.c. per minute.

Metaraminol (Aramine) is the newest of the vasopressor agents. Milligram for milligram it is about 1/20 to 1/25 as potent as Levophed.[107] As has been demonstrated with Levophed,[108-110] Aramine acts directly on the heart to increase myocardial contractility, cardiac output, and coronary blood flow, in addition to contracting the peripheral vascular bed.[111,112] It has the advantage of being nonirritant, so that it can be administered subcutaneously, intramuscularly, and intravenously. Thus, tissue infiltration will not cause a slough. While its vasopressor effect is not as prompt as Levophed, its duration of action is more prolonged, so that plugging of the needle will not result in an immediate fall in blood pressure.[107,113,114] It may be used, therefore, to advantage when prolonged intravenous therapy is necessary.

Combatting arrhythmias is essential for relief of shock, since conversion to sinus rhythm may in itself restore a normal blood pressure. This may be accomplished by those vasopressor agents which improve blood flow through the coronary arteries. If the arrhythmia persists in spite of vasopressor therapy, the usual measures for combatting specific arrhythmias are indicated. In some instances shock may be accentuated by the presence of marked bradycardia.

Atropine, given intravenously in doses of 1 mg., has been found useful in blocking vagal tone and elevating the heart rate. When heart block exists, isopropylarterenol (Isuprel), used in conjunction with Levophed, has been found to be an effective agent.[90,115] It is administered intravenously in intermittent doses of 0.02 to 0.04 mg., or in an infusion containing 1.2 to 2 mg. in 500 c.c. of 5 per cent glucose in water. It also may be given sublingually in tablets of 15 mg. In resistant patients, the use of the Zoll external cardiac pacemaker may be indicated in order to increase the heart rate. Parenteral steroids also have been reputed to alleviate heart block secondary to acute myocardial infarction, probably by reducing the inflammatory swelling,[116,117] although Lown and associates[118] demonstrated that adrenal steroids also exert a direct accelerating effect on atrioventricular conduction.

The use of steroids for the management of coronary shock has been suggested because of the benefit observed in other forms of shock,[119] and because of the reported potentiating effect on vasopressor drugs.[120] However, no significant benefit has been observed with steroids in coronary shock. In our series, intravenous hydrocortisone failed, in 15 patients, to improve a poor response to Levophed. Similarly poor results were reported by Griffith and associates,[115] who used cortisone as an adjunct medicament in 12 patients. Sampson[37] states that "The corticoids have been disappointing in the treatment of shock in myocardial infarction." On the experimental side, Williams and associates[121] failed to find any difference in the arteriolar vasoconstriction produced by norepinephrine in normal and in cortisone-treated rabbits.

While it has been shown that congestive heart failure is not necessary for the occurrence of coronary shock, it frequently coexists, particularly when shock has been present for several hours. It is often difficult to decide that congestive heart failure has been added to the picture of severe shock. Evidence of pulmonary edema may be produced by shock alone.[122] Elevation of peripheral venous pressure can be produced by the venoconstriction associated with shock.[86,123] The circulation time may be prolonged in the absence of congestive heart failure when shock is present.[124] While the heart size is normal or reduced in shock and increased with heart failure, the change may not be recognizable or may be masked by pre-existing enlargement. Serous effusions and significant peripheral edema are evidences of congestive heart failure but require time for development. In general, it is found that distinct neck vein distention, peripheral venous pressures over 20 cm. of water, and a rise of venous pressure of 5 cm. of water on hepatic compression (avoiding the Valsalva phenomenon) are reliable indications of heart failure. Further, shock alone rarely produces severe pulmonary edema. When these signs are present, it is wise to digitalize the patient intravenously in divided doses, using such cardiac glycosides as Cedilanid. Where rapid digitalization is mandatory, ouabain administered intravenously has proved most useful. An initial dose of 0.5 mg., followed at hourly intervals by 0.1 mg. until approximately 0.8 mg. total is injected, is the accepted mode of administration.

Evidence has been given that in some patients the shock state may result in part from a failure of the vasoconstrictor impulses to compensate for the falling cardiac output. In animals, blocking the afferent sympathetic pathways from

the heart has been effective in elevating the blood pressure by raising TPR or potentiating the effect of vasopressor drugs. Adequate clinical trial of this procedure is lacking as yet. However, we have used thoracic epidural analgesia, following the technique described by Bromage,[125] in 4 patients whose shock failed to respond to all other measures. With the dose of Levophed unchanged, epidural analgesia produced a significant pressor response in 3 of these patients; 2 of the patients were relieved of shock and 1 patient survived. Since the mortality of patients who fail to respond to all other measures, including large doses of vasopressor drugs, is uniformly 100 per cent, any salvage from this group is significant. The experimental background for epidural analgesia and the initial clinical results appear sufficiently promising to warrant further trial. It is to be hoped that some specifically acting drug yet will be discovered to accomplish a similar result.

DISCUSSION AND CONCLUSIONS

More than a decade ago, Boyer[8] wrote a critical review of cardiogenic shock which exerted great influence on the concept of this disorder. From the laboratory and clinical experience then available, he concluded, "It appears, therefore, that the bulk of evidence both direct and theoretical, is overwhelmingly in favor of the concept that shock in myocardial infarction is largely, and probably solely, a manifestation of heart failure." Recently, he stated, "Whatever has transpired since that time, both from personal experience and from medical reports, has served to strengthen, rather than alter, this view."[9]

Fishberg and associates,[6] on the other hand, wrote in 1934, that "The fall in arterial pressure is due not only to the weakness of the left ventricle but also to the peripheral circulatory failure of shock. Apparently the latter is usually the more important of the two factors." Yet, so confused did the issue become that Fishberg himself later reversed his opinion.[7] Since then a considerable body of work has accumulated in the clinic and the experimental laboratory, but the controversy over heart failure versus peripheral circulatory failure is still joined. This controversy, particularly as it concerns coronary shock, is reflected most clearly in the confusion which exists in the treatment of this important clinical syndrome. It would seem appropriate to reappraise the situation in the light of recent investigative data.

It is well to point out that until 6 years ago there was no experimental method for studying protracted severe coronary shock in the experimental animal, and it is only within the past decade that cardiac output studies by the Hamilton[126] dye method could be performed on human beings. From a clinical standpoint also, the subject has been clouded by the wide variance of criteria for the evaluation of both the severity of the shock and the efficacy of the therapeutic agents used.[90]

In a discussion of the physiologic changes which contribute to the production of coronary shock it would be well to attempt an answer to each of the following questions:

I. *Does a fall in blood volume explain the occurrence of shock?* It has been demonstrated that in severe shock either no blood volume reduction or maximum reduction of 16 per cent occurred both in human beings and in dogs. These

changes in blood volume cannot alone account for the occurrence of shock, since it is well recognized that approximately 40 per cent of the circulating blood volume must be lost before severe shock occurs.[84-86]

II. *Does marked acceleration of heart rate account for the shock?* This possibility can be eliminated for these reasons: (1) It is known that heart rates of the order of 180 are necessary for the production of significant hypotension.[52] In human beings severe coronary shock may exist with sinus rates of 120 or less. Of 82 severely shocked patients in our previously reported series,[90] 71 had heart rates of 120 or less. (2) Experimental coronary shock can be produced, utilizing the plastic microsphere injection technique, in the absence of significant changes in heart rate.

III. *Is coronary shock due solely to the amount of heart muscle damaged?* Since 1862, investigators[62,63] have been examining the effects of various types of injury to heart muscle. These methods have produced ventricular fibrillation and congestive heart failure, but only irregular and transient reductions in blood pressure, despite massive destruction of heart muscle.

As has been detailed above, animal studies in which coronary shock was produced have shown no correlation between the occurrence of shock and the extent of myocardial infarction, the fall in cardiac output, or the pressure changes in the heart chambers. In fact, greater degrees of myocardial damage frequently have been produced without shock than have been produced when shock occurs.

Clinical studies of the hemodynamic changes in coronary shock have shown reductions in cardiac output which are usually severe but which often are no greater than in patients without shock.

It is clear from the animal and human data that the amount of heart muscle damaged or the degree of reduction in cardiac output are often not the sole explanations for the occurrence of coronary shock.

IV. *How is total peripheral resistance related to the occurrence of coronary shock?* In the animal experiments described above, the principal difference between the shocked and nonshocked dogs was a marked rise in TPR in the nonshocked group and little change in TPR in the shocked group of animals.

The hemodynamic studies in human coronary shock indicate that these patients may fall into one of two groups, i.e., those in whom the cardiac insult is so great that even marked vasoconstriction cannot maintain the blood pressure, and those in whom failure of homeostasis is added to the basic myocardial injury so that the TPR remains unchanged. The hemodynamic changes in the latter group of patients is thus in complete agreement with the data in the animal experiments, in which a similar failure of homeostasis was found. It should be stressed that neither the animal experiments nor the human data have shown "peripheral vascular collapse," if this term is used to mean over-all vasodilatation and an appreciable fall in TPR. The abnormality which is present, and which has been overlooked by those who deny the presence of a peripheral factor in coronary shock, is the failure of the TPR to rise in the face of a falling cardiac output and blood pressure.

Animal experiments and clinical observations of the last few years have not supported the concept that heart failure is an essential part of coronary shock.

The available evidence points to the existence of peripheral mechanisms, not directly linked to the degree of myocardial damage. Whether these mechanisms are largely reflex or hormonal, or probably both, further research promises a greater reduction in the mortality of coronary shock.

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Book Reviews

PULMONARY EMPHYSEMA. Edited by Alvan L. Barach, M.D., and Hylan A. Bickerman, M.D., Baltimore, 1956, Williams & Wilkins Co., 545 pages, illustrated. $10.

This volume was compiled with the assistance of 18 distinguished authors, all of whom have made significant contributions to our knowledge of emphysema within the last 10 years. The very fact that a book of this size can now be compiled on the single subject of pulmonary emphysema, testifies to the considerable volume of clinical experimental work which this disease has received in the last 10 years. This book provides an excellent summary of contemporary knowledge and opinions concerning chronic respiratory disease.

Of the 18 chapters which comprise the volume, 5 are concerned with various aspects of respiratory physiology in emphysema, 3 with a discussion of the role of infection in emphysema and with descriptions of senile emphysema and pathogenesis, and the remainder discuss various aspects of the treatment of established pulmonary emphysema. The arrangement of these chapters appears to be rather arbitrary, and the volume would have benefited from a somewhat different arrangement of these sections. The general reader would be well advised not to read the book in the sequence in which the chapters are written, but to read first the sections on respiratory physiology, and then the chapters discussing the physiologic basis of therapeutic procedures. The possible benefit of breathing exercises and of diaphragmatic exercises in emphysema can only be intelligently understood and discussed in relation to the alterations in the mechanics of breathing found in this disease. Yet, the chapter (which is an excellent one) on the mechanics of breathing is placed 175 pages after the chapter on diaphragmatic function and breathing exercises.

It is not possible to discuss in detail the individual points of view expressed by the authors of some of the chapters. The sections on treatment are perhaps not sufficiently critical, and the physician who is particularly interested in this disease will look in vain for carefully controlled clinical trials of the therapeutic procedures advised. As is well known in a condition such as emphysema, the degree of bronchial obstruction may vary considerably from month to month, and perhaps even from day to day, and the therapeutic success of any procedure will depend inevitably on the relative importance of potentially reversible factors in any individual patient. If it be accepted that the main or distinguishing lesion in emphysema is loss of parenchymal lung tissue, which no amount of therapy can yet restore, then the assessment of the value of individual therapeutic procedures depends greatly on the selection of patients and on a number of extraneous factors, all of which must be most carefully controlled if reliable conclusions are to be drawn. The sections on therapy in this volume are clearly written by authors who have had considerable practical experience in the maneuvers they recommend, but it is not possible to say yet that a completely convincing case has been made for the therapeutic value of every one of the different measures proposed. From this point of view, a volume of this type, comprehensive though it is, represents an interim stage in the development of our knowledge of this condition. The major puzzle of the etiology of emphysema remains unsolved. The difference in sex incidence is completely unexplained, and, although in the last 10 years we have acquired a great deal of fundamental physiologic knowledge about the condition when fully established, we have yet to understand entirely the relationship of the disease to the changes in the lung that inevitably occur with increasing age. One may look forward to the day when the various therapeutic maneuvers suggested have been tested completely, and in the light of detailed physiologic studies either are found to be valid or are discarded. Until that has been done under controlled circumstances, the value of some of the therapeutic procedures advocated in this volume with considerable enthusiasm will remain a matter of opinion.

The whole book has been carefully edited. The standard of figures, diagrams, and x-rays is high, and each chapter has an adequate bibliography. This volume fills an important gap in the literature on emphysema, in that it provides a readable and up-to-date summary of contemporary opinions and knowledge. It deserves to be read widely, and it is not too much to say that the knowledge and outlook incorporated within it should be a part of the normal educational background of any physician or surgeon interested in chest disease.

D. V. B.

ATLAS OF CLINICAL ENDOCRINOLOGY. By H. Lisser, M.D., and Roberto F. Escamilla, M.D., St. Louis, 1957, C. V. Mosby Co., 476 pages, 148 plates. Price $18.75.

The authors of the *Atlas of Clinical Endocrinology* have succeeded in bringing together a vast experience in clinical endocrinology. They have done this by drawing heavily on photographs of patients, on their x-ray investigations, and on the pathologic specimens whenever these were available. In addition, they have reproduced charts depicting the salient laboratory features in the patients and the disease state under discussion. There certainly can be little or no argument about the general divisions of the endocrine disorders discussed, but undoubtedly there will be differences of opinion regarding nomenclature. Such semantic difficulties are not exclusive to clinical or research endocrinology. The appendix which concerns itself with growth and developmental patterns, as well as with behavior manifestations, is invaluable; it is unusual to find these summarized in a short section.

Undoubtedly, this atlas will be of great value to many physicians who have only an occasional opportunity of seeing endocrine problems, as well as to specialists in other fields in which endocrinology may play an ancillary role.

J. C. B.

CORONARY HEART DISEASE. By Milton Plotz, M.D., New York, 1957, Paul B. Hoeber, Inc., 353 pages.

Since coronary heart disease is ubiquitous in Americans, it is entirely fitting that a book should be written concerning it. Dr. Plotz has presented a very complete treatise on the subject. There are 21 chapters, each with an excellent bibliography. It is my belief that Dr. Plotz has been successful in attempting to summarize the present status of coronary heart disease, and that he has done so by writing a carefully organized and easily comprehended book, using numerous illustrations and tables.

Although coronary heart disease is extremely common, the symptoms of this disease frequently are overlooked or misinterpreted. Accordingly, I believe that this book should be read by medical students, general practitioners, internists, and cardiologists.

J. W. H.

SCHRIFTENREIHE DER ZEITSCHRIFT FÜR DIE GESAMTE INNERE MEDIZIN. (Cardiologie IV, Heft 7) Prof. Dr. Theodor Brugsch, Editor, Leipzig, 1956, Georg Thieme, 192 pages, 43 illustrations.

The volume consists of 5 papers, the first 4 of which are based on a large amount of the experimental material of the authors, together with a quite detailed literature review of the various fields. R. Behre studied the important question of objective experimental documentation of subjective cardiovascular symptoms, comparing 102 patients having primarily organic heart disease with 194 patients having primarily functional disorders (pp. 7-84). All methods used were comparatively simple and applicable in a clinical diagnostic laboratory, or even in a physician's office; they included venous pressure (at rest, during Valsalva, and after mild exercise), vital capacity (rest and exercise), breath holding time, circulation time, Schellong's functional test (essentially changes of pulse rate and blood pressure in standing and exercise), ECG (rest,

exercise, standing), and x-ray. None of these methods gave a significant differentiation between the 2 groups of patients, perhaps with the exception of the ECG which was abnormal in 50 per cent of the patients with organic heart disease and in 3.2 per cent of the patients with functional disorders. The author holds that the response of the ECG to exercise (abnormal in 66 per cent of patients with organic heart disease, and of 7.8 per cent of patients with functional disorders) and to standing (abnormal in 16.5 and in 37.4 per cent, respectively) is diagnostically superior to the resting ECG, but these figures do not bear out his conclusion for the orthostatic test (which would miss the majority of patients in both groups). As negative as the results essentially are, it is important that such an attempt was made and reported.

W. Blumenthal discusses the clinical significance of the residual air determined from the planimetric measurement of the thorax area in x-ray films (pp. 85-113). Particularly valuable was the relative residual air in per cent of the total capacity, calculated from the difference of the thorax area in inspiration and expiration, minus a correction factor of 20 per cent. There was a significant correlation between the relative residual air and maximum voluntary pulmonary ventilation. A value of the relative residual air of 50 per cent seems to be a critical dyspnoe threshold, and a value of 55 per cent, a threshold for prolongation of the lung-ear circulation time. Decrease of the relative residual air up to 50 per cent may have little or no functional consequence.

A. Dittmer found the protein fractions of diagnostic value particularly in acute myocardial infarction (pp. 114-145). There was a significant increase of the alpha 2, alpha 1, and beta globulin fractions in the first 2 days of infarction, and a later decrease with healing. In fatal infarction, the increase of these fractions was progressive. The investigations of the author, however, also include other types of cardiac pathology. In animal (frog heart) experiments and clinical material, W. Jenke found a synergistic effect of digitalis and nitrates, and an antagonistic effect between nitrates and catecholamines (pp. 146-182). H. Kanitz and F. P. N. Schennetten studied in 6 patients with cardiac decompensation the effect of rectal administration of G-strophanthin (pp. 183-193).

E. S.

Announcements

THE THIRD INTERNATIONAL CONGRESS OF THE INTERNATIONAL SOCIETY OF ANGIOLOGY will be held in the Ambassador Hotel, Atlantic City, N. J., Oct. 18 to 21, 1957. Address: Dr. Henry Haimovici, Secretary-General, 105 East 90th St., New York 28, N. Y.

THE ELEVENTH ANNUAL MEETING OF THE AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS will be held on Nov. 2, 3, and 4, 1957, in the Grand Ballroom of the Hotel Knickerbocker, Chicago, Ill. Address: Dr. O. J. Pollak, Secretary, P. O. Box 228, Dover, Delaware.

THE MOUNT SINAI HOSPITAL OF CHICAGO offers a one-year approved RESIDENCY IN CARDIOLOGY. The training is integrated with that of the Division of Cardiology of the Chicago Medical School.

Applicants should have completed a three-year residency in medicine, or a two-year residency in medicine or pediatrics plus one year in cardiology.

Inquiries should be addressed to Dr. Aldo A. Luisada, Director, Division of Cardiology, 2755 West 15th Street, Chicago 8, Illinois.

On Oct. 17 and 18, 1957, a SEMINAR ON HEART SOUNDS AND MURMURS with particular reference to the diagnosis of congenital and rheumatic heart disease will be held in Burlington, Vt. Among the guest speakers will be Drs. A. A. Luisada and A. S. Nadas. This event is sponsored by the Vermont Heart Association and the University of Vermont College of Medicine. Further information may be obtained from Dr. E. Lepeschkin, Burlington, Vt.